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Organizational Pattern of a complete chapter As far as possible this structure has been followed in each chapter

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CHAPTER 5

ADRENALS

PRECLINICAL

CLINICAL

CLINICAL ENDOCRINOLOGY

VOLUME TWO

CLINICAL ENDOCRINOLOGY

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TWO VOLUMES
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VOLUME TWO



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SECTION 45

PRELIMINARY

I HISTORY

Before the Christian Era		Castration was practiced for many centuries and results were recognized
About 1400 B C[69]		Testicular tissue was recommended for impotence[69]
384 322 B C	Aristotle	Castration effects in birds, beast and man were described
777 837	Mesue the Elder[43]	Testicular extract prescribed as aphrodisiac
1664	Willis[0]	Blood receives a special ferment from the spermatic veins
1667	Hamen and van Leeuwenhoek[6]	Sperm cells seen for first time
1668	De Graaf[15]	Lobular architecture of the testicle was demonstrated
	Spallanzani[6]	Fertilization occurred by direct contact of spermatozoa and ova
1762	John Hunter[31]	First experiments on transplantation of testes in the fowl were performed
1762	Pott[53]	Recognition of hydrocele
1786	John Hunter[30]	Secondary sexual characteristics in birds and descent of testes in humans were described
1799(?)	John Hunter[3]	Successful artificial insemination of a woman
1830	Cooper[13]	Epididymis of a dog contained active sperm 6 years after ligation of vas
1841	von Kolliker[67]	Sperm declared to be of cellular origin
1849	Berthold[1]	First to prove internal secretion of testes normal cock instincts were produced in capons by testicular grafts
1850	Leydig[37]	Interstitial cells were described
1865	Schweigger Seidel[60]	Spermatozoon possesses nucleus and cytoplasm
1865	Sertoli[8]	Spermatids attach to special supporting cells during their development
1877	Malassez,[40] Monod and Arthaud[44]	Chorionepithelioma discovered
1889	Brown Séquard[7, 8]	Effects produced by self administered testicular extracts (from dogs and guinea pigs) were reported
1891	Poehl[2]	A substance, spermin isolated from testes
1893	Groffith[5]	Degeneration of testicle by replacement within abdominal cavity (dogs)
1894	Ramm[54]	Castration used as a therapeutic measure for treatment of prostatic hypertrophy
1895	Florence[19]	Test for detection of spermatic fluid
1896	Reinke[56]	Crystalloids of interstitial cells found
1899	Bevan[4]	Operation for undescended testicles first performed
1899	Sellheim[61]	Delay in union of epiphyses noted in capons
1903	Albers Schonberg[1]	Certain amount of x ray or radium exposure over testes caused sterility
1903	Bouin and Ancel[5]	Removal of one testis from a rabbit produced hypertrophy of the interstitial cells in the remaining one, suggesting hormonal secretion

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INTRODUCTION

Skin manifestations of a disease of another organ or an organ system may be *specific* or *nonspecific*

Specific dermadromes contain the same pathological elements which cause or characterize the lesions of the disease in another part of the body system Skin metastases of a malignant tumor of the stomach repeat the adenomatous structure of the primary growth Leukemic infiltrations of the skin consist of the typical leukocytes of the leukemia and hematogenous tuberculosis of the skin is still as much tuberculosis as it was in the tubercular focus from which it descended

Much more frequently the dermadromes are *nonspecific* Neither anatomy nor course seem to repeat the primary disease The pruritus in Hodgkin s disease sweating in tuberculosis or in arsenic poisoning are such nonspecific manifestations They are cutaneous responses to pathologic stimuli and since the means of expression which the skin possesses are limited heterogeneous causes may produce identical skin symptoms Pruritus perspiration erythema pigmentation hypertrichosis allergic inflammation keratosis are some words from the language in which the skin answers if it is provoked It follows that a conclusion as to the underlying condition from a nonspecific symptom like pruritus alone is not possible In other words the nonspecific dermadromes are *not diagnostic* they are merely *suggestive* of a diagnosis They have to be weighed together with other manifestations to make a diagnosis possible Naturally this limits the practical value of the knowledge of the cutaneous symptoms of internal disorders However the same is true of the symptomatology of all other fields A diagnosis is usually not based on one specific symptom but rather on a characteristic pattern formed by a *variety* of nonspecific manifestations

Another fact increases the difficulty Hardly one dermadrome is an *invariable* companion of an internal disorder The melanosis in Addison s disease is missing in a considerable percentage of the cases Pruritus commonly encountered in Hodgkin s disease diabetes gout arsenic poisoning may be absent Even the rash in measles or chicken pox may not appear Jaundice in obstruction of the common duct seems to be one of the few inevitable dermadromes

Before entering the discussion of the skin manifestations of internal disorders the reader might well ask which *criteria* permit the assumpton of such a relationship

There is no doubt about the relation of the specific dermadromes to the internal companions to which they are *subordinated* as is the case in focal infection or *coordinated* as in syphilis For the investigation of the status of the nonspecific dermadromes the statistic method is the most important one If pruritus is associated with diabetes in a larger percentage than with a normal control

group, we are justified in calling pruritus a dermadrome of diabetes. This apparently simple method naturally has all the fallacies connected with statistics. The number of cases must be sufficiently large. The character of the material must be considered. For example, in the case of diabetic pruritus it is important whether the patients are hospitalized or ambulatory, controlled or uncontrolled diabetics, wealthy or poor. The control group must be large and its character should correspond to the probed group of diabetics in age, sex, racial and social make-up, etc. It is of greatest importance whether observations have been gathered from records which had been written by another physician or whether they have been collected by the author himself with the purpose of his investigation in mind. Generations of interns may not have paid much attention or at least may not have entered a note on the presence or absence of pruritus or epidermophytosis in the diabetic patients. Then a man becomes interested in the question and he starts to ask patients and to make notes. This may cause the apparent incidence to soar.

If *rare* dermatoses occur in association with relatively rare internal diseases, the relationship can be accepted if a few cases only have become known. Examples are the few instances of dermatitis herpetiformis after total parathyroidectomy or cutis verticis gyrata in acromegaly or acanthosis nigricans in visceral carcinoma.

Other criteria of a relationship between a dermatosis and an internal disorder are disappearance of the former following successful treatment of the latter as it occurs in some cases of hypertrichosis of ovarian origin. The close parallelism between the ups and downs of the disease and the skin changes is sometimes a good evidence of a relationship. This can be observed in the dermatoses of the legs which sometimes accompany periods of circulatory decompensation.

Skin Manifestations of Internal Disorders

Chapter I

THE DERMADROMES OF SYSTEMIC INFECTIONS

Hematogenous or Metastatic Infections * Microbids (Bloch[17])

The ectogenous infections of the skin for example impetigo erysipelas and the superficial mycoses do not belong to the subject of this book If however the micro organisms travel with the blood stream from an infectious focus in the system to the skin and cause there corresponding manifestations of the infection the resulting dermatosis is a dermadrome of the systemic infection and requires discussion

When as far back as 1915 J Jadassohn*[8] gave this definition of hematogenous skin infection he wisely chose the word corresponding He was aware of the fact that the hematogenous infections are not identical with the primary lesion They differ more or less although a relationship can usually be found The various hematogenous infectious lesions the microbids (Bruno Bloch) or the ids for short have been shown to have a number of common features The study of the experimental hematogenous infection of the guinea pig with fungi proved particularly instructive for the understanding of the pathogenesis of the microbids in general

Experimental Hematogenous Fungus Infection —Saeves[18] in J Jadassohn s clinic in Berne Switzerland was the first to show that a single intracardial injection of an emulsion of spores of *Achorion quinckeanum* and *Trichophyton gypseum* can produce in the guinea pig several crops of fungi containing clinically typical skin lesions These mycotic lesions healed spontaneously after about three weeks The hematogenous skin infections differed little from primary skin infections The animals developed a generalized specific skin allergy toward fungi just as they did after ectogenous infection The hematogenously produced lesions appeared to have a certain predilection for shaved or traumatized[19] sites

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* The hematogenous infections of the skin have been studied intensively by Joseph Jadassohn and Bruno Bloch and their schools

[17] Bloch B Les microbides cutanés Arch dermato-syphiligr Hôp St Louis 4 157 194 193

[18] Saeves J Experimentell Beiträge zur Dermatomykosenlehre Arch f Dermat u Syph 121 161 1915

[19] Kogoj F Lokalisationsbestimmung hämatogener Infectionen Arch f Dermat u Syph 150 333-355 19 6

M Sulzberger[20] then in Bloch s clinic could show that no actual mycotic granuloma of internal organs could be produced by intracardial injection of *Achorion quinckeanum* in spite of the presence of fungi in the spleen and in other organs The histologic examination of hematogenous skin lesions demonstrated that the fungi could be found mainly in the stratum corneum and in the hairs not in living tissues[21] leaving no doubt about the *elective localization* or *dermatropism* of certain microbes

Foci—The *foci* from which the microbes may enter the blood can be found in many organs Streptococcic and staphylococcic foci are known to occur in dental granulomas in abscessed teeth and in many other organs The lungs and the mediastinal lymph nodes may be the foci for the hematogenous spread of tuberculosis The skin itself may be the site of primary foci which are able to emit fungi tubercle bacilli and other microbes into the system Trauma inflammation with hyperemia and suppuration (kerion) fever and intercurrent infections like colds or influenza are likely to have an influence on the *mobilization* of microbes from a primary focus X ray treatment of a primary trichophytic lesion and injection of trichophytin are named among the factors which have been seen to provoke trichophytids[21] The traumatization of gonorrheic infiltrates or tuberculous tissues may cause a crop of hematogenous skin infections All infectious processes which lead to erosion of blood vessels and lymphatics may lead to metastatic infection Jadassohn[2] stresses the importance of all influences which weaken the systemic resistance The possibility of a release of bacteria from a silent focus into the blood stream apparently without any of the known causes must be considered

The *presence of microbes in the blood* in cases of microbids has been demonstrated for fungi by M Jessner[23] and others [4] and for tubercle bacilli by Kren and Lowenstein[25] Konrad[26] and others Many similar findings especially of pyogenic bacteria are known

Metastatic Sites—The experimental fungus infection shows that the microbes do not stay and develop wherever they are deposited by the blood stream The fungi prefer the keratinized tissue other microbes favor other sites Tuberculids are seen most often on the extremities especially the legs probably due to the tendency to stasis in the extremities Some epidermophytids have a special tendency to form eczematoid epidermophytids in the palm Traumatized or inflamed areas attract fungi spirochetes pyogenic bacteria or

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[20]Sulzberger M Pathogenesis of Trichophytids The Spontaneous Passage of Formed Elements From the Primary Lesion Into the Circulating Blood Arch Dermat & Syph **18** 891 901 1928

[21]Bloch B Allgemeine und experimentelle Biologie der Dermatomykosen Handb d H u Gk **11** 300 377 1928

[22]Jadassohn J Importance of Immune Biologic Processes in Morphology of Skin Lesions Arch Dermat & Syph **21** 35 1930

[23]Jessner M Trichophytid Zbl **11** 449 1924

[24]Bloch B Die Trichophytide Handb d H u Gk **11** 564 19 8

[25]Kren O and Löwenstein E Die Bedeutung der Bazillämie bei den verschiedenen Formen der Hauttuberkulose und bei Lupus erythematodes Arch f Dermat u Syph **166** 375-389 1932

[26]Konrad J Demonstration of Tubercle Bacilli in Circulating Blood (Löwenstein Method) Dermat Ztschr **66** 30-37 1933

tubercle bacilli The appearing of syphilitic papules in areas of friction and maceration is well known [18,19,7]



Fig 1 —Trichophytid (Courtesy Division of Dermatology Department of Medicine University of Chicago)

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[7] Jadassohn W Tl re p im nt ll Untersuchung n über hämatog ne traumatisch bedingte Hauttube kulose Arch f D rmat u Syph 159 3 4-333 1930

Common sites of microbic deposits are the vascular nets which surround the *hair follicles*. Hematogenous follicular rashes (lichens) are well known in mycoses, syphilis, tuberculosis and other diseases. J. Jadassohn[8] suggested that the fungi in the blood stream like to settle in the follicles because of the close relation to the hair, their preferred medium. Microbic metastases in the capillary loops of the *papillae* may cause scarlatiniform rashes, roseola or papules. Those in the *subcutis* produce nodules of all sizes. The *larger blood vessels*, especially in the subcutis, are another target. Thus reticulated livedo racemosa-like forms may ensue, as is occasionally seen in syphilis. The *veins* may be the origin of deep nodules in late syphilis. J. Jadassohn[8] felt that these infections originating in the walls of veins (Wolters[9]) do not stem directly from the blood in the veins but rather from the blood in the *vasa vasorum*. Thus the point of attack contributes to shape the clinical pictures, of which lichenoid follicular rashes, roseola and erythema nodosum are the main representatives.

Other Characteristics of Hematogenous Skin Infection.—Perhaps even more important than the site of the microbic metastasis is the *allergic response* of the skin. Almost always some allergy has already developed when from the primary focus of infection microbes are disseminated through the circulation. The specific skin reactions are mostly positive. Bloch[17] and other authors have seen fresh crops follow injections of specific allergens. The allergic reactions in hematogenous skin infections may, though frequently strong, be weak or negative, as suggested by the so-called anergic tuberculids. In other instances of weak allergy the metastatic lesion shows features of a primary infection, that is, greater abundance of microbes and nonspecific inflammation. Miliary tuberculosis and early syphilis are examples. As the immune biologic reaction grows in strength, fewer germs and increasingly tuberculoid histologic structures will be found. This is the case in tuberculosis lichenoides, in tuberculoid leprosy, in leishmaniasis and especially in the late stages of syphilis. Syphilids are rich in spirochetes when the luetin allergy is lacking and poor when it is present. Not only the skin may have changed its specific reaction, since there are many indications that the microbe itself may have become allergic in the course of its contact with the host. For instance, spirochetes and other protozoa may become resistant to previously effective drugs.

General *septic symptoms* like malaise, chills and fever and swelling of the lymphatic nodes and joints may accompany the crops.[17]

The general course of hematogenous infectious skin eruptions is usually benign. There is a marked tendency to spontaneous involution, as is the case in some tuberculids.

The *distribution* of hematogenous infectious dermatoses exhibits some characteristic features. One would expect that microbes which invade the blood stream, especially the pulmonary veins and the large arteries, would land in fairly even distribution in the entire skin. This is not always the case. Syphilitic

[8] Jadassohn, J.: Hematogenous Infectious Diseases of the Skin, Arch. Dermat. & Syph. 21 5 6 538, 1930.

[9] Wolters, M.: Lupus nodularis hämatogenen Ursprungs, Arch. f. Dermat. u. Syph. 69: 83, 1904.

roseola the acute exanthems and other blood borne infections in spite of the great number of individual lesions show modifications in their distribution caused by peculiarities of the terrain Other examples of uneven dissemination are the circumoral pallor in scarlet fever the predilection of the upper half of the body in variola and varicella the often exclusive localization of papulonecrotic tuberculids on the extremities and of some trichophytids on the palms Of course symmetric dissemination and the appearance in crops as seen in secondary syphilids or in acute exanthems suggest hematogenous infection but asymmetry does not rule it out The sarcoids and tertiary syphilis are usually asymmetric Paucity of microbes in the blood stream or paucity of those germs which can succeed in setting up a hematogenous skin infection may explain the lack of symmetry

Pyogenic Focal Infection —The hematogenous skin infections from streptococcic or staphylococcic foci particularly in the teeth and tonsils have so far not found the same interest among dermatologists as the corresponding manifestations in the other organs among other specialists It appears that there exist two groups of investigators who do not seem to know much of each other the dermatologists with the microbids on one side and the proponents of the classical focal infection on the other The former frequently show a skeptical attitude toward the achievements of the latter who in turn often ignore the work of dermatology in this field *

Both schools struggled with the question of whether toxic products of microbes are able to produce specific dermadromes or whether hematogenous infection with living germs is a necessary prerequisite

Today the importance of the question has diminished since it is known that toxins from microbes may produce lesions similar to those of living bacteria and that absence of microbes in microscopic and cultural tests does not prove that the questioned lesions are not caused by germs J Jadassohn[31] emphasized on several occasions the clinical similarities of many hematogenous toxic and hematogenous infectious dermatoses Purpura is an example of a dermadrome common in infections as well as in poisonings

From the pathogenesis of the tuberculids and trichophytids which are more often infectious than toxic and also from other observations we may conclude that the secondary foci are likely to be of a bacteremic and metastatic nature although bacteria are rarely found in the secondary skin lesions

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* The last comprehensive review of the field of focal infection by Gutzeit and Parade[30] (1939) with a bibliography of about 1 [illegible]00 items does not mention the names of J Jadassohn B Bloch nor those of their pupils And this in spite of the fact that most of these authors worked for a long time in the same block in the University Hospital in Breslau Germany

[30] Gutzeit K and Parade G W Focal Infect Ergebn d inn Med u Kinderh 57 613 7 1939

[31] Jadassohn J Hämatogen Dermatosen Zbl 35 60[illegible] 1931

The conception of focal infection is based on the work of Passler [32] Hunter [33] Billings [34] and, particularly Rosenow [35] but the older literature also contains much material pointing in the same direction The term *focal infection* (focus of infection) was coined by Billings[34] who defined it as a circumscribed area infected with pathogenic microorganisms and usually communicating with a mucous or cutaneous surface causing secondary foci through various ways especially through the blood stream Later the definition became more precise Focal infection may now be defined as a *disease caused by a chronic focus of infection which harbors pathogenic microorganisms and though often dormant itself continuously or continually causes remote symptoms* (modified after Gutzeit and Parade) [30] The teeth and the tonsils are the main sites of the primary foci [35] followed in frequency by the paranasal sinuses the middle ear the bronchi the uterus and



Fig [illegible] —Focal infection Sudden and often recurrent crops of acute circumscribed erythema of the cheek Attacks ceased entirely after extirpation of chronically infected appendix

adnexa the prostate the intestinal tract and some other less common sites like varicous ulcers and bronchiectases Rosenow [37] to give an example found tonsillary foci in 51 per cent of his patients with arthritis and in 74 per cent of those designated as having infective lesions of the skin In the latter group 77 per cent had infected teeth

[32] Pässler H Ueber die Beziehungen einiger septischer Krankheitszustände zu chronischen Infectionen der Mundhöhle Verhandl d deutsch Gesellsch f inn Med 26 Kongr p 321 1909

[33] Hunter W Role of Sepsis and Antisepsis in Medicine Lancet 1 77 1911

[34] Billings F Focal Infection Lane Medical Lectures New York 1916 D Appleton & Co

[35] Rosenow E C Zusammenfassung der Forschungsergebnisse über Fokalinfektion und elektive Lokalisation Med Klin 27 325 1931

[36] Rössle R Ueber Fokalinfektion Verhandl d deutsch Gesellsch f inn Med Kong 51 455-486 1939

[37] Rosenow E C Herdinfektion und elektive Lokalisation Verhandl d deutsch Gesellsch f inn Med Kong 42 408 1930

The *bacteria* which cause focal infection are predominantly streptococci especially the viridans type although staphylococci *Escherichia coli* gonococci and others also have significance Billings[34] and Rosenow[35] showed that the streptococci in the living tissue of the primary foci can change their characteristics in various ways There were changes in virulence changes in cultural behavior and even transition into other forms for example from streptococci into pneumococci The observations on character and extent of such mutations are still controversial but the majority of the bacteriologists recognize them in principle The explanations for the emission of bacteria into the circulation in crops have been mentioned in the first half of this chapter The finding of streptococci in the blood[35] is relatively infrequent and there are many series of observations with entirely negative results The probability of finding small numbers of bacteria in the blood is small The paucity of germs in the blood distinguishes focal infection from true sepsis It is well that Billings[34] changed the misleading term oral sepsis to focal infection

A most controversial subject was and still is Rosenow s[37] theory of the *elective localization* of the microbes especially the streptococci Rosenow,[37] who considers the assumption of an elective localization as basic in his work showed in a very large series of controlled experiments that streptococci isolated from primary foci had a surprising tendency to produce lesions in animals which corresponded to the secondary lesions seen in the patients from whom the strain was derived Thus for example streptococci isolated from teeth and other primary foci in 1 539 cases of ulcers of the stomach and duodenum produced in 65 per cent of the animals which had been infected intravenously comparable stomach or duodenal lesions Other examples of elective localization are the tendency of green producing streptococci to produce lesions in the cardiac valves and of hemolytic streptococci to localize in the joints The percentages in which lesions could be produced in the rabbit were mostly around 60 often higher rarely lower Thus in 60 per cent of nine cases of erythema nodosum and of twenty nine cases of herpes zoster comparable skin lesions were produced in the rabbit These findings were startling The experiments were most expertly executed and the numbers of cases and controls for example 723 cases of arthritis 206 cases of ulcerative colitis were large One would think that Rosenow s[37] impressive material should have settled the question of elective localization in a positive sense once and forever However while confirmations were forthcoming[38] many investigators among them men who had been trained by Rosenow failed to corroborate his results or obtained smaller percentages[39] Particular care was taken by Von Albertini and Grumbach[40] These authors could find no definite proof for the existence of an organotropism of the streptococci They believe that the individual resistance of the animals and not the selective organotropism of the microbes decides whether a localized abscess or a generalized sepsis will follow the injection of

[38] Haden R L and Jordon W H Multiple Onychia as a Manifestation of Focal Infection Arch Dermat & Syph 8 31 36 19 3

[39] Azzi Azzo Focal Infection Schweiz med Wchnschr 71 1365-1366 1941

[40] Von Albertini A and Grumbach A Focal Infection Schweiz med Wchnschr 68 1309 1938

cultures The authors emphasize the fallacies resulting from comparing secondary lesions in an animal which had not been infected before and which receives a single massive dose of bacteria with secondary infection in man where the dissemination of microbes probably occurs continually and allergy has had a chance to develop Von Albertini and Grumbach s[40] experiments did not deal with skin diseases The role of specific *allergy* in streptococcal infections has been demonstrated and emphasized by many observers In proper concentration skin tests with autogenous vaccine can be made and therapeutic effects reached Humoral antibodies have been demonstrated However agglutination precipitation and other tests with hyperimmune sera which had proved of great value in Rosenow s hands have not been found suitable by other authors because of the pronounced tendency of the streptococci to spontaneous agglutination [40] Intercurrent infections climate menstruation nutrition endocrine and other factors may also modify the allergic reactions

Diagnosis —Many authors stress the importance of a history of frequent colds recurring tonsillitis [3] postnasal dripping occasional stiff neck myositis arthritis transitory tenderness in various joints neuritis endocarditis appendectomy and other episodes of pyogenic infections Of course the history only suggests focal infection and it constitutes good grounds for a careful investigation [40]

The collaboration of dentists rhinologists and radiologists is often needed Specimens for culture should be taken from the depth not from the surface This is especially important with regard to the tonsils and the teeth The most suitable medium for cultures seems to be Rosenow s brain broth From the isolated strains a vaccine may be made and intracutaneous skin tests done These tests are difficult to interpret and controls are necessary Various laboratory *methods to demonstrate humoral antibodies are used by some authors* but they have not gained general acceptance [41] The demonstration of an infectious focus does not prove that the dermatosis in question is caused by the focus

The hematologic methods as well as exact thermometry may give hints with regard to the existence of an infection Gutzeit and Kuchlin[42] determine the blood sedimentation rate and expose the area suspected of an active focus to ultra short waves An exposure of seven minutes is used for teeth and twelve minutes for the tonsils An increase of the sedimentation rate two to four hours after the provocation is supposed to indicate activity of the focus in question The patient should be fasting The value of the method is still controversial since other authors obtained similar reactions from normal teeth The advantage of the test is that it is based on the objective phenomenon of the sedimentation rate and not on more or less vague exacerbations of pain or other sensations It seems that no absolutely reliable test for the activity of a focus has been devised

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41 Ayres S Jr and Anderson N P Focal Infection in Dermatology Arch Dermat & Syph 34 421-431 1936

42 Gutzeit K and Kuchlin W Beitrag zur dentalen Infektion und ein neuer Weg in ihrer Diagnosestellung durch Kurzwellenprovokation München med Wchnschr 84 961 965 1937

Treatment —So far the best evidence to prove the causal relationship between a lesion in the skin (or elsewhere) and a focus of infection is the therapeutic effect of the elimination of the alleged focus But even here great skepticism is necessary to prevent post hoc ergo propter hoc conclusions since many of the conditions in question for example rosacea eczema and lichen planus take an irregular course with frequent remissions and exacerbations *Penicillin* and the sulfonamides are the first drugs to be tried The eradication of dental tonsillar and other foci by surgical means should be attempted The removal of one accessible focus does not rule out the existence of other inaccessible or undetected foci Some foci like endocarditic or aortic granulations are beyond the surgical reach or would involve formidable operations which are not warranted Conservative topical methods include local disinfectant and cleansing procedures like swabbing and gargling but they will hardly influence encapsulated foci in the depths of tonsillary crypts The treatment with autovaccine from the recovered strains should be tried but many authors are skeptical Ayres Jr and Anderson[41] recommend gradually increasing intravenous injections of the vaccine Nonspecific protein injections may be tried cautiously but there is some danger of producing reactions in hyperergic patients General procedures like the salt free diet of Gerson Sauerbruch, and Hermanndorfer hydrotherapy and ultraviolet light have been recommended Acute exacerbations following such apparently harmless treatments as mud baths are known Severe exacerbations have been observed occasionally after surgical treatment of foci for example arthritic exacerbation following extraction of infected teeth or new crops of gonorrheic keratoses after dilatation of a urethral stricture[43] Ayres Jr and Anderson[41] give a long list of dermatoses suspected to be caused by focal infection Most of the alleged conditions bear remarks like some cases or occasionally intimating how little solid ground the imposing work has yielded for dermatology In the following list which is in part after Ayres Jr and Anderson[41] the dermatoses are grouped according to the validity of the arguments claiming focal infection in their pathogenesis

GROUP I

The nature of the dermatosis as a hematogenous infection or toxic manifestation is well established in

Syphilis
Leprosy
Tuberculosis
Acute exanthems
Septic pyemids
Erythema nodosum
Trichophytids and other mycosid for example in blastomycosis
Tularemia
Keratoderma blennorrhagicum
Typhoid fever
Acute exanthematous diseases and many other rashes in infections

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[43] Shuster M Relationship of Arthritis to Oral Diagnosis Defocalisation and Streptococcus Vaccine Therapy Am J Orthodontics 27 149-156 1941

Group II

Focal infection has been shown or suggested with more or less good reasons in some cases of

- Acne rosacea[44,45]
- Herpes zoster[34,35,45]
- Erythema elevatum diutinum[46]
- Lupus erythematosus acutus disseminatus[47]
- Generalized telangiectasis[48,49]
- Acrodermatitis continua[50]
- Angioneurotic edema and urticaria[51]
- Alopecia areata[45]
- Acne vulgaris (some cases of severe involvement)[52,53]
- Dermatitis herpetiformis[52,54]
- Pemphigus[54]
- Nonmycotic vesicular eruptions of the hands and feet
- Purpura
- Sycosis vulgaris
- Eczema[52,53,55,58]
- Dyshydrosis[58]
- Lichen chronicus simplex[52]
- Chronic paronychia[8]
- Pyodermic ulcerations in chronic ulcerative colitis[59]
- Erythemas of various kind[5]
- Lichen planus[60]

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[44] Felt H La slo E A and Vero F Rosacea as a Bacte id From Focal Infection J A M A **105** 1738 1935

[45] Barber H W Dental Infection and Di ease of the Skin P oc Roy Soc Med **20** 39-48 19?7

[46] Weidman F D and B sançon J H Erythema elevatum diutinum Arch Dermat & Syph **20** 593 19 9

[47] Madden J F Acute Dis em nated Lupus Erythemathosus Arch Dermat & Syph **25** 854 1932

[48] Ayres S Jr Burrows L A and Anderson N I Generali ed Telangiectasia and Sinus Infection Arch Dermat & Syph **26** 56 1932

[49] Becker S W Gen ralized Telangiecta ia Arch Dermat & Syph **14** 387 19 6

[50] Barber H W and Eyre J W H Acrodermatitis continua (Hallopeau) or Dermatitis Repens (Crocker) B it J Dermat **39** 485 1927

[51] Semon H C Some Cutan ous Effect of Dental Sep is Lanc t **202** 889 891 192?

[52] Richter W Focal Inf ction Dermat Wchnsch **109** 911 915 1939

[53] Hunst in W Dentaler Foku und Hautkrankheit n Tübingen Dis ertation 193?

[54] Welsh H L Specificity of a St eptococcus I olated From Patients With Pemphigus Arch Dermat & Syph **30** 611 1934

[55] Visher J W Focal Infections in th Etiology of Ec ema Am J M Sc **170** 7 3 7 7 19 5

[56] Gomes A A Eczema and D ntal Diseas Brit M J **2** 590 19 6

[57] Memmesheim r A M Fokale Inf ction und chronisch s Ekzem Arch f D rmat u Syph **167** 183 195 19 9

[58] Kémeri D Ursachen d Dyshyd o en und Ek me Dermat Wchnschr **91** 1615 1619 1930

[59] Jankel on I R and Mas H B F Pyogenic Skin Lesions Accompanying Chronic Ulcerative Coliti Am J Dig t Di & Nutrition **3** 19 1936

[60] Robert H L Focal Infection Brit J Dermat **33** 319 334 3 3 373 1921

Chapter II

SYSTEMIC INFECTIONS

Pyogenic Septicemia

Bacteremia does not necessarily produce clinical symptoms If the microbes enter the blood stream in small numbers or only once the natural bactericidal power of the blood often disposes of them quickly as illustrated by postoperative bacteremia If the blood is repeatedly or constantly fed with microbes from a focus of infection such syndromes as discussed under tuberculosis gonorrhea or focal infection may ensue The massive presence of bacteria in the blood together with the outstanding clinical symptoms of characteristic fever or wasting is called septicemia or sepsis If the development of multiple ab ces es is an outstanding feature as is often seen in staphylococcic septicemia the term pyemia is often used The term toxemia should be reserved for those conditions which are caused by bacterial toxins such as diphtheria tetanus and botulism

The bacteria causing sepsis in two series of 150 and 255 cases[61] were found to be *Staphylococcus aureus* in 36 5 per cent *Streptococcus hemolyticus* in 36 per cent and various types of pneumococci in 5 5 per cent The rest of the list predominantly contains other types of staphylococci streptococci and the Friedlander bacillus In other large series the staphylococcic cases outnumber the streptococcic cases 2 1 or 3 1[62]

Otitis carbuncles and related conditions are listed (20 per cent)[61] as the most common source of sepsis others being operation (14 per cent) infections of the genitourinary tract (9 per cent) paranasal sinuses (6 per cent) liver and gall bladder (4 per cent) and miscellaneous (19 per cent) The on et is often sudden occasionally with a evere chill and fever Chills and spiking temperatures occur in about one half of the cases Sustained low fevers are common and seem to entail a higher mortality[61] Usually the bacteria can be isolated from the blood Endocarditis and metastatic abscesses are the most characteristic complications and causes of death

Hemolysis hemoglobin staining of the lining of the blood vessels abscesses particularly of the lungs reddened and hypertrophic bone marrow cloudy swelling of the kidneys liver and heart and a moderately enlarged and very soft spleen are the ordinary post mortem findings

Since the introduction of the sulfonamides the mortality rate has dropped from 67 to 54 5 per cent[61] in staphylococcic septicemia alone from 82 to 74 per cent[63] The advent of penicillin has probably reduced the mortality still further

[61] Neuhof H and Aufses A H Pyogenic Sepsis 255 Cases Surg Gynec & Obst 77 544 552 1943

[62] Mendell T H Staphylococcic Septicemia 35 Cases Arch Int Med 63 1068 83 1939

[63] Skinner D and Keefer C S Significance of Bacteremia Arch Int Med 68 851 875 1941

Dermadromes —In contrast to the importance of the skin as a cause the dermadromes of septicemia are neither very common nor important compared with the severity of the general septic syndrome There seem to be some distinguishing features between the staphylogenic and streptogenic hematogenous skin lesions (pyemids) [64 65]



Fig 3 —Acute streptogenic septicemia Universal exanthem of grouped follicular hemorrhagic lesions Back

Staphylogenic Pyemids —Pyemids occur in about one third of the cases of staphylogenic sepsis [6 66] They are probably more common than those caused by streptococci [67] *They appear suddenly often with chills and fever heralding* a turn for the worse [68] They often start with rashes consisting of macular or urticarial lesions vesicles umbilicated pustules, or bullae [69] The tendency to epidermolysis is considered by some authors a characteristic but inconstant [64] feature of staphylogenic pyemids [70] Petechiae are seldom absent [70] Metastatic subcutaneous nodules and abscesses in varying sizes and depths may especially in infants give the impression of furunculosis [71] Mendell [62] saw metastatic ab

[64] Fuchs D Pyämische Dermatitiden (Pyämide) Handb d H u Gk 9 2 449 472 1934
[5] Robinson S Septicemia Fruptions Urol & Cutan Rev 41 490-49? 1937
[66] Felsenthal W Ueber Staphylokokkensepsis Mitt a d Grenzgeb d Med u Chir 42 18 262 1930
[67] Fraenkel F Metastatische Dermatosen bei akuten bakteriellen Allgemeinerkrankungen Arch f Dermat u Syph 129 386 403 19 0
[68] George P and Giroire H A propos des faits nouveaux de staphylococcémies Presse méd 34 611 19 6
[69] Strandberg J Ein Fall von vesicopustulösem Pyämid Arch f Dermat u Syph 111 83 1910
[0] Davis T B Septicemia Practitioner 147 545-5 7 1941
[71] Finger E Dermatitis pyaemica Wien klin Wchnschr 9 54? 548 1896

scesses in the skin occur in 30 per cent of thirty five cases of staphylogenic septicemia Nodules which do not form abscesses may resemble erythema nodosum[7] (McCrea after M Barber [4])



Fig 4 —Femal A ute staphylog nic s pti emia aft r furuncle Erythema and scaling



Fig 5 – A ut taphyl genic pti emia Eryth matou erupti n

Erythemas of varying shape and extent sometimes clinically identical with true scarlet fever [4] sometimes roseolar or exudativ multiform[75] (Bloemen and Scalongne [5]) but also papules vesicles pustules nodules and petechiae may be seen simultaneously Ulcerations are rare

Ba b H W O al Infection and Di ases of th Skin C u a Ho j R j 77 1 140 1957
[7] Barbe M Staphylococcu Albu S ptic mia Brit M J 1 40 409 191
Dohm n A Scarlatiniform Exanth m in Inf ctions With Staphylococcus Aur us Hemolyticu Klin W hnschr 17 1689 1693 1938
[75] Bloem n J J and Scalongn H W M ta tatisch staphylog ne D rmatosen D rmat Wchnsch 110 477 48 1940

The histologic findings are in line with the clinical picture Edema and vesicles of the epidermis miliary abscesses and papillary capillaries stuffed with cocci and surrounded by leukocytes are the dominant features

Streptogenic Pyemids —Pyemids are reported to occur earlier in the course of streptogenic septicemia than the corresponding staphylogenic eruptions They also often start as macular sometimes morbilliform or scarlatiniform exanthems sometimes as less numerous or solitary erysipeloid patches[67] (Werther and others after Fuchs[64]) Papular and papulopustular[75] or bullous eruptions[76] are not rare Most authors emphasize the hemorrhagic tendency of the streptogenic eruptions Petechiae especially on the lower legs on the buccal mucosa and on other sites are common They may become vesicular or bullous In the mouth small yellow specks may be seen on the petechiae [70] Erythema nodosum [77] erythema multiforme [65] and local gangrene and ulceration have been described although the tendency to suppuration is much less pronounced than in staphylogenic lesions Microscopic examination reveals dense streptococcic emboli in the small vessels particularly in the vasa vasorum [71] surrounded by leukocytic infiltrations The damage to the vascular wall is demonstrated by the extravasation of red cells together with cocci

Sabouraud (Kitchevatz[78]) is reported to have postulated a staphylo streptogenic dermatosis analogous to the trichophytids and epidermophytids Of course he meant a hematogenous infection originating from a pyoderma and not from septicemia which in his days was already well known A lichen pyodermicus after widespread pyoderma formed by acuminate micropapules[79] and resembling lichen trichophyticus or lichen scrophulosorum and also other benign pyodermids have been described under various names although general recognition is still lacking

It is true that within certain limits the various microbids resemble each other M Favre[80] observed in patients with furuncles and impetigo lichenoid lesions and squamous seborrhoic plaques sometimes resembling pityriasis rosea The author saw in a case of acute pustular acne vulgaris superficial pink lesions which at their edges consisted of very small dull papules These lesions disappeared when the acne eruption quieted down A series of thirty cases of strepto staphylotoxids the largest so far was presented by Kitchevatz [78] He too saw pyodermids after widespread streptodermas or deep ulcerating staphylodermas The streptopyodermids which often originate from rhagades behind the ear itched more and were about five times as common as the staphylo pyodermids Kitchevatz[78] saw erythematous spots which resembled syphilitic roseola scarlatiniform or lichenoid rashes vesicular papular and erysipelatous

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[76] Nicolas J Moutok H and Caté J Septicopyohémie streptococcique avec éruption pemphigoïde Provinc méd Paris 24 101 103 1913 abstracted in Dermat Wchnschr 58 131 1914

[77] Biber t in H and Fischer M Ein Erythema nodosum—ähnlich s gutartig verlaufend s Pyämid Arch f D rmat u Syph 149 07 1925

[78] Kitchevatz M Strepto-staphylococcies cutanées Intern Derm Kongr Kopenhagen 1930

[79] Schreus H T and Coehl F Lich noide Fruptionen b i Pyod rmien (Lichen pyod rmicus B merkungen über Komplementablenkung im Blute b i Staphylokokk n und Trichophytieerkrankungen Wirkung d r Röntg nstrahlen Dermat Ztschr 31 273 81 19 0

[80] Favre M Angiodermite pigmentée et purpurique Nouvelle pratique dermatologique Vol V Paris 1936 Ma on & Ci pp 413-430

lesions and erythematous and herpetiform enanthemas There were also focal reactions and the appearance of new lesions after autogenous vaccines and toxins This relatively large amount of material has not found much attention Occasionally benign pyodermids [81] circinary or annular exanthems[8] and acne necrotica resembling embolic infarctions have been recorded after various primary pyogenic infections Balog[82] saw primary staphylogenic skin infections followed by disseminated semiglobular later umbilicated papulopustules which appeared in crops and subsided with the cure of the primary focus The embolic bacterial character of these benign pyemids could be demonstrated More corroboration is needed however The same is true of the claims[83] that various types of eczema among them nummular eczema, are secondary pyodermids and that nonmycotic pustular eruptions of the hands and feet are pyodermids [84]

In the *treatment* of all pyemids penicillin must be tried first

Subacute Bacterial Endocarditis, Endocarditis Lenta (Jaccoud Osler's Disease)

The streptococcus viridans which is the most common cause of subacute bacterial endocarditis probably stems from focal infections of the teeth paranasal sinuses and tonsils [85] The streptococci produce vegetations on the heart valves especially in patients with congenital or rheumatic heart disease The vegetations cause fever bacteremia myocarditis glomerulo nephritis and embolic metastases There is a great variety of nervous hematologic and other symptoms The onset is gradual After an early nondescript subfebrile stage of increasing malaise the disease develops into a severe illness with many septic complications and ends fatally after several months in over 90 per cent of the cases A small minority reaches a bacteria free nonactive stage which too terminates fatally from valvular disease and cardiac decompensation [85] Penicillin in high doses over many weeks seems to be effective [85a]

Dermadromes —About one third of the sufferers from subacute bacterial endocarditis are anemic and very pale and later jaundiced (90 per cent) [85] *Sweating* is an annoying symptom *Petechiae* well known to occur in other streptococcic infections are common In an analysis of eighty eight cases they were found in the skin in 60 per cent [86] in the mucosae in 14 per cent and in the retina in 11 per cent The petechiae appear in crops and sometimes have pale yellow or necrotic centers [85 87] Petechiae under the nails are stretched to

[81] Bošnjakovi S Sev ral Forms of Chronic Pyod rmia Lij čn vj s 54 261 267 1932 Zbl 42 6 2

[82] Balog P Benign Embolic Pyemid J Invest Dermat 5 107 1942

[83] Krzy ztalowic F Fczema From Pyogenic Infection Przegl dermat 24 208-224 19 9 Zbl 32 91 1930

[84] Andrews G C and Machacek G F Pustular Bacterids of the Hands and Feet Arch. Dermat & Syph 32 837 84 19 5

[8] O ler W and Chri tian H A P inciples and Practice of Medicine d 15 New York 1944 D Appl ton C ntury Company Inc

[85] Fleming A Penicillin Its Practical Application Philad lphia 1946 The Blakiston Co

[86] Middl ton W S and Burke M St eptococcus Viridans Endocarditis Lenta Am J M Sc 198 301-3 3 1939

[87] Guldberg F Dermatosis in Endocarditis Venerol 8 51 53 1931 Zbl 41 78



Fig 6 —Sul acut bacterial ndocarditis l urpura



Fig 7 —Subacut ba t rial ndocarditi l urpuric ra h

short lines by the growing nail and are often called *splinter hemorrhages* Petechiae about the nails resemble paronychia but they fail to come to a head [88] If they have central blisters they resemble erythema multiforme [89] Other varieties of these eruptions have been described as papular or lichenoid [90] maculo

[88] E chbach H É uption cutanée et endocardit infectieuse prolongée Bull et mém Soc méd d hôp de Pa i 54 97 299 1930

[89] Soutt r Manif tations cutané s dan l endocardite lente Zbl 35 45 1931

[90] Weissenbach R J Martineau J and Bris t J P Manifestations cutanées de la maladi de Jaccoud Osle Bull Soc f anç de dermat et syph 39 1688 1701 193

papular and purpuric [91] or subcutaneous and nodular (Osler's nodes). They sometimes prefer the extensor surfaces, sometimes the palms and soles (Janeway lesions).

These eruptions heal spontaneously. Petechiae on the rectal or sigmoid mucosa are supposed to be an early diagnostic sign in subacute bacterial endocarditis.[92]

Rheumatic Fever

Rheumatic fever[85, 93, 94] is an infection probably caused by hemolytic streptococci. Hereditary and constitutional factors as well as exogenous factors like exposure to cold, damp climate, and youthful age, favor the infection. The outbreak often starts with pharyngitis, tonsillitis, and tender joints. Chills usher in the fever, which is high but does not follow as regular a pattern as in



Fig 8.—Rheumatic nodules

scarlet fever. Acute arthritis involving one joint after the other is the center of the clinical picture. Endocarditis, anemia, and more rarely pleurisy, iritis, chorea, and encephalitis may appear. While the mortality in the early stages does not exceed 3 per cent,[85] the frequent cardiac damage plays an important part in the mortality in later life.

The pathologic findings are characterized by small, widespread, circumscribed granulomatous nodules which are most often found in the ventricular walls of the heart (Aschoff bodies) and in the walls of many arteries, especially of the aorta and the coronary, and in the periarticular tissues.

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[91] Libman, F, and Sack, B: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Arch Int Med 33: 701, 19[illegible]

[92] Fei[illegible]n, J: Intestinal Petechia as Diagnostic Sign in Subacute Endocarditis, Internat Clin 2: 57-67, 1941

[93] Leichtentritt, B: Acute Articular Rheumatism, in Pfaundler and Schlossmann: Diseases of Children, Vol III, Philadelphia, 1934, J B Lippincott Company, pp 357-375

[94] Leichtentritt, B: Die rheumatische Infektion im Kindesalter, Ergebn d inn Med u Kinderh 37: 1-99, 1930

Dermadromes —The skin participates in the syndrome in various ways *Pallor* is common The skin of the extremities frequently becomes glossy and there may be redness of the palmar eminences The palms are moist The repeated *sweating* often causes miliaria especially on the chest and the inner surfaces of the arms *Petechiae* and other hemorrhagic signs have often been observed Keil[95] saw them in 10 per cent of 523 cases Recently[96] it has been demonstrated that children with rheumatic fever generally show a low capillary resistance especially in late winter and before barometric depressions



Fig 9 —Cutan subcutaneous rheumatic nodules about the olecranon

Urticaria occurs in the early stages[97] *Erythema nodosum* has often been linked to acute articular rheumatism[98 101] but the evidence is scant and there is a modern tendency to deny any relationship[99] The observation that such recognized rheumatic diseases as endocarditis and chorea are seldom connected with erythema nodosum has been interpreted as evidence against its rheumatic character[100] (Kassowitz after Leichtentritt[94])

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[95] Keil H Rh umatic Erythema Ann Int Med 11 2246 1938

[96] Brown E E and Wa son V P Capillary Resi tance in Rheumatic Children J Pediat 18 3 8-336 1941

[97] Traub Erich Ueber die Bed utung der Hauterscheinungen beim akuten Gelenkrheumatismus Ztschr f Kin l rh 58 769 780 1937

[98] Hadl y H G Dermatos s of Rheumatic Fever Urol & Cutan Rev 45 713 714 1941

[99] Keil H Relation of Eryth ma Nodosum and Rheumatic Fever Ann Int Med 10 1686 1937

[100] Feer F Zur A tiologie des Eryth ma nodo um Schwei med Wchnschr 66 68 685 19 6

Erythema multiforme[101 104] sometimes appears with exacerbations of the ar ticular disease

The erythemas in rheumatic fever seem to have been over classified from a morphological viewpoint It is sufficient to distinguish between nodular papular and erythematous rheumatic skin manifestations Transitional forms exist Keil[95] found 181 eruptions among 523 cases of rheumatic disease Be sides more or less nonspecific dermatoses like hemorrhagic eruptions telangi ectases urticaria scarlatiniform exanthems in approximately 10 per cent of the cases rheumatic erythemas and in 7 per cent subcutaneous nodules could be found Erythema nodosum is not included

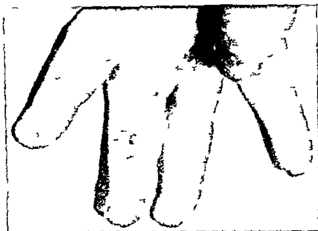


Fig 10 —Cutaneous rh umatic nodules (From Ros nberg W A Arch D rmat 1934)

The *rheumatic nodules* (rheumatismus nodosus) appear in crops more often in the subcutaneous tissues than in the cutis itself[105] They vary from mustard seed to olive size They are movable nontender and covered with normal skin They are most often found over the olecranon about the elbow joint over the knuckles and other bony eminences for example over the forehead and along the crest of the vertebrae The nodules are often symmetrically distributed par ticularly on the limbs The rheumatic nodules must be regarded as indicating activity of the rheumatic infection which means an unfavorable prognosis[94 97 106] Other rheumatic lesions especially rheumatic heart disease are almost always

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[101] Singer G Die Hautveränderungen b im akuten Gelenkrh umatismus neb t B merkungen über Erythema multiforme Wien klin Wchn chr 10 841 844 1897

[102] Müller Theodor Ein eryth matös bullös-pustulöse Exanthem bei Polyarthritl acuta Dermat Ztschr 62 269 274 1931

[103] Meyer August Akut r Gelenkrheumatismus mit E ythema pustulo um Ztschr f klin Med 117 413-4 4 1931

[104] Richon J Girard J and Picard D Un cas d érythème multiforme au cours de la maladie de Bouillaud Bull Soc franç de dermat et syph (Réunion dermat Nancy) 45 1760-1763 1938

[105] Rosenberg W A Cutaneous Rh umatic Nodul s Arch Dermat & Syph 30 377-384 1934

[106] Struth rs R R and Bacal H L Significance of Rh umatic Nodul s in Childhood Canad M A J 46 376-381 191

present and the mortality is as high as 31 per cent[107] Recently less pessimistic opinion on the prognostic significance of the rheumatic nodules have been voiced[108] It has even been said that the appearance of rheumatic nodules may indicate the subsiding of the particular rheumatic incident though not of the disease[106] Histologically they correspond to the Aschoff nodules of the myocardium Leichtentritt[94] succeeded twice in isolating streptococcus viridans from excised nodules In a third case he and Biberstein[94] found cocci in microscopic sections

The rheumatic nodules must be interpreted as true infectious metastases The rheumatic nodules usually heal occasionally they may take on the appearance of chronic hard almond sized subcutaneous cystic tumors in the neighborhood of the large joints especially the elbow Such nodosities which are well known in other infectious diseases particularly spirochetoses are called juxta articular nodules[109 110 111] H Hoffmann[110] however in his comprehensive monograph on juxta articular nodes does not believe that rheumatic fever plays a part in the etiology of these lesions

Cutaneous rheumatic nodules[10] are much rarer than subcutaneous ones They have been observed on the fingers and palms as red not painful slightly indistinct papular lesions which do not ulcerate They consist of perivascular infiltration with endothelial proliferation In later stages giant cells develop[112]

Rheumatic papular erythema is a discrete red eruption of small papules mainly but not exclusively about the articulations Keil[9] found it in 3 per cent of his 523 patients with rheumatic fever Like other rheumatic eruptions it appears in crops Keil[9] separates erythema marginatum with polycyclic and raised borders from papular erythema Much more significant and better known than the papular eruptions i the flat *annular erythema*[113] which is so characteristic and so intimately connected with rheumatic infection that it can be called a specific rheumatic dermatosis The incidence given by various authors varies widely Erythema annulare is still considered a rare complication which seldom occurs more frequently than in 10 per cent of children with rheumatic fever[97] (Wallgren after Traub[97]) although Leichtentritt[94] and Lehndorff and Leiner[113] give figures higher than 60 per cent These differences may be largely caused by the type of clinical material because erythema annulare is mainly a dermadrome of rheumatic disease in children with endocarditis The rash starts with pale bluish pink maculae of only a few millimeters in diameter These spots soon blanch in the center and spread peripherally with an active but not infiltrated margin Thus polycyclic or zigzag often rather thin almost linear figures result

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[107] Hayes R M and Gibson S Rheumatic Nodules in Children J A M A 119 554 555 1942

[108] McCulloch H in Discussion of Struthers R R and Bacal H L Rheumatic Infection in Childhood Sedimentation Rate and Schilling Count Am J Dis Child 52 1031 1936

[109] Hopkin H H Subcutaneous Nodules of the Juxta Articular Type Bull John Hopkins Hosp 49 5-16 1931

[110] Hoffmann H Juxtaartikuläre Knoten Handb d H u Ck 12 1 419-498 193

[111] Katz C Juxta articuläre Knoten bei Gelenkrheumatismus Ztschr f klin Med 129 363 1936

[112] Gadrat J Rheumatismal Papulous Erythema Dermal Lesion of Aschoff Klinge Nodul Type Case Bull Soc franç d dermat et syph 41 1788 1788 1931

[113] Lehndorff H and Leiner C Erythema annulare Ein typisches Exanthem bei Endokarditis Ztschr f Kinderh 32 46 53 19 ?

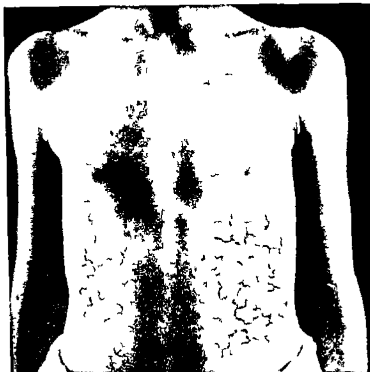


Fig 11 —Eryth ma annulare heumaticum (Courtesy D Arthu F Abt)



Fig 1 —Eryth ma a nulare rh umaticum (Cou tesy Dr Erich Urbach)

The lesions which appear most often on the chest less often on the abdomen back and extensor surfaces of the limbs are delicate not infiltrated not scaly not tender and do not itch The erythema has not been observed on the mucous membranes It appears in one or several crops, and the individual crops usually last two to five days [93]

Since the eruptions may follow each other in short intervals the patient may have erythema for years The rash may easily be overlooked Leichtentritt[93] found erythema annulare always connected with rheumatic endocarditis or chorea and he emphasizes its ominous significance Other authors do not share his pessimistic interpretation [97 114] but all agree that it has not been seen in endocarditis of nonrheumatic character

The biopsy[115] shows neutrophilic infiltration as a main characteristic Bacteria have not been found in the lesions Lowenstein[116] and his group were able to cultivate the tubercle bacillus from the blood of one case of rheumatic fever with erythema annulare This finding still lacks confirmation The eruption is now regarded as an expression of cutaneous allergy [117]

Still s disease is a chronic articular disease of childhood Fever generalized lymphadenitis and splenic tumor are outstanding features *Streptococcus viridans* has been demonstrated in the blood by Leichtentritt [94] Periarticular papules and erythematous eruptions have been reported [95]

Palindromic rheumatism is a disease characterized by often recurring relatively short attacks of arthritis [118] Although there is no connection with rheumatic fever intracutaneous and subcutaneous nodules mainly on the fingers have been described in some cases The nodules were mostly short lived rarely persisting over a long period

Periarteritis Nodosa

Periarteritis nodosa[119] is characterized by multiple inflammatory destructive foci in the walls of the smaller arteries which may lead to aneurysm and other severe circulatory disturbances The clinical picture varies according to the area which is predominantly involved Males outnumber females 3 1 [120] Age is not a decisive factor Acute infectious diseases of many kinds have often been observed to precede the outbreak of periarteritis nodosa The onset is usually though not always rapid Repeated attacks and exacerbations often characterize

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[114] Abt A F Erythema Annulare Rheumaticum Am J M Sc 190 824 1935

[115] Carol W L L and Van Krieken J A Histopathologie des Erythema annulare von Lehndorff und Leiner Acta paediat 17 372 1935

[116] Löwenstein Ernst Die Tuberkelbazillämie in ihrer Auswirkung auf die Gesamtmedizin Mit einem klinischen Teil von Carl Reitter Wilhelm Neumann und Otto Kren Leipzig und Wien 1936 Franz Deuticke

[117] Urbach E and Bleier A Erythema Annulare Rheumaticum (Lehndorff Leiner) Case Arch Dermat & Syph 41 515 5 0 1940

[118] Hench P S and Rosenberg E F Palindromic Rheumatism Proc Staff Meet Mayo Clin 16 808-815 1941

[119] Kussmaul A and Maier R Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa) die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung inhergeht Deutsches Arch f klin Med 1 484 1866

[120] Harris A W Lynch G W and O Hare J P Periarteritis Nodosa Arch Int Med 63 1163 118 1939

the course In more than 90 per cent of the cases the outcome is fatal after less than one year In a review of 101 pathologically confirmed cases Harris Lynch and O Hare[1 0] listed as significant symptoms and signs fever (80 per cent) leukopenia up to 5 400 (70 per cent) renal manifestations like albuminuria (64 per cent) abdominal pain (27 per cent) cylindruria (46 per cent) hyper tension (64 per cent) edema (52 per cent mostly of cardiac distribution) loss of weight hematuria and neuritis Thoracic pain dyspnea headache and vertigo are common The diagnosis is usually made post mortem However with better knowledge of the dermadromes and greater number of biopsies the disease is being recognized more frequently during life[1 0 1 1 1]

The *cause* of the disease is not known but it has nothing to do with syphilis as was early suggested It is striking that periarteritis nodosa has so often de veloped shortly after or even in immediate connection with various infectious diseases especially those caused by hemolytic streptococci While the staphy lococcus the meningococcus and the gonococcus are on the list of bacteria which have been found in close association with periarteritis nodosa[1 5] the streptococcus is by far the most frequent one A correlation to rheumatic fever with Aschoff bodies and verrucous endocarditis was discovered in four of Spiegel s[1 5] seventeen cases and in one of Rothstein and Welt[133] The clinical course often suggests septicemia The coincidence with well established allergic states and also ex perimental evidence of infection[134] suggests allergy as an important pathogenic factor in periarteritis nodosa[135]

The *treatment* is symptomatic In one case sulfapyridine together with acetylcholine seemed to be curative[1 2]

Dermadromes —Cutaneous manifestations occur in about 25 per cent[1 0 1 3] In rare instances almost exclusive involvement of the skin without participation of the internal organs has been observed[124 125] The case material permits a tentative grouping[1 1 6] into nodular erythematous and hemorrhagic eruptions

The most characteristic element is the periarteritic *nodule* which may be found in or under the skin These nodules have been noted in roughly 25 per cent of the cases but they probably often have escaped observation The lesion is very seldom larger than a pea more often smaller In hemorrhagic cases the nodules may reach the size of a robin s egg[1 7] or larger and may become cystic and blood filled *The nodules which have been seen to appear in crops in various* stages of the disease are hardly ever more than fifty in number In order of frequency they have been observed on the forearm chest legs abdomen

131 Vining G W Periarteritis Nodosa Arch Dis Childhood 13 31 44 1938

132 Legro J Periarteritis Nodosa or Kussmaul Maier Disease First Case Diagnosed in Infant During Life Recovery From Therapy With Sulfapyridine and Acetylcholine Arch Françaises de Pédiat Paris 2 117 118 1944 1945

123 Ketron L W and Bernstein J C Cutaneous Manifestations of Periarteritis Nodosa Arch Dermat & Syph 40 9 9 944 1939

12 Matras A Zur kutanen Form der Periarteritis nodosa Wien klin. Wchnschr 61 991 1938

125 Spiegel R Periarteritis Nodosa Arch Int Med 58 993 1936

126 Boyd L J Periarteritis Nodosa Cutaneous Symptoms Bull New York M Coll Flower & Fifth Ave Hosps 3 175-18 1940

127 Alkiewicz J Multiple nekrotisierende Periarteritis nodosa der Haut mit Acanthosis nigricans Arch f Dermat u Syph 168 5?? 1933

The lesions, which appear most often on the chest less often on the abdomen back and extensor surfaces of the limbs are delicate not infiltrated not scaly not tender and do not itch The erythema has not been observed on the mucous membranes It appears in one or several crops and the individual crops usually last two to five days [93]

Since the eruptions may follow each other in short intervals the patient may have erythema for years The rash may easily be overlooked Leichtentritt[93] found erythema annulare always connected with rheumatic endocarditis or chorea and he emphasizes its ominous significance Other authors do not share his pessimistic interpretation [97, 114] but all agree that it has not been seen in endocarditis of nonrheumatic character

The biopsy[115] shows neutrophilic infiltration as a main characteristic Bacteria have not been found in the lesions Lowenstein[116] and his group were able to cultivate the tubercle bacillus from the blood of one case of rheumatic fever with erythema annulare This finding still lacks confirmation The eruption is now regarded as an expression of cutaneous allergy [117]

Still s disease is a chronic articular disease of childhood Fever generalized lymphadenitis and splenic tumor are outstanding features *Streptococcus viridans* has been demonstrated in the blood by Leichtentritt [94] Periarticular papules and erythematous eruptions have been reported [95]

Palindromic rheumatism is a disease characterized by often recurring relatively short attacks of arthritis [118] Although there is no connection with rheumatic fever intracutaneous and subcutaneous nodules mainly on the fingers have been described in some cases The nodules were mostly short lived rarely persisting over a long period

Periarteritis Nodosa

Periarteritis nodosa[119] is characterized by multiple inflammatory destructive foci in the walls of the smaller arteries which may lead to aneurysm and other severe circulatory disturbances The clinical picture varies according to the area which is predominantly involved Males outnumber females 3 1[120] Age is not a decisive factor Acute infectious diseases of many kinds have often been observed to precede the outbreak of periarteritis nodosa The onset is usually though not always rapid Repeated attacks and exacerbations often characterize

[114] Abt A F E ythema Annulare Rh umaticum Am J M Sc **190** 824 1935

[115] Carol W L L and Van Krieken J A Histopathologie des Erythema annulare von Lehndorff und Leiner Acta paediat **17** 372 1935

[116] Löwenstein Ernst Die Tube kelbazillämie in ihrer Auswi kung auf die Gesamtmedizin Mit einem klinischen Teil von Carl Reitter Wilhelm Neumann und Otto Kren Leip ig und Wien 1936 Franz Deuticke

[117] Urbach E and Blei r A Erythema Annulare Rheumaticum (Lehndorff Leiner) Case Arch D rmat & Syph **41** 515-520 1940

[118] Hench P S and Ros nberg E F Palindromic Rheumatism Proc Staff Meet Mayo Clin **16** 808 815 1941

[119] Kussmaul A and Mai r R Ueb r ein bisher nicht beschri bene eigentümliche Arteri ner krankung (P riarteritis nodosa) die mit Morbu B ightii und rapid fort chreitender allgemeiner Muskellähmung einhergeht D ut ches Arch f klin M d **1** 484 1866

[120] Harris A W Lynch C W and O Hare J P Periarteriti Nodosa Arch Int Med **63** 1163 1182 1939

the course In more than 90 per cent of the cases the outcome is fatal after less than one year In a review of 101 pathologically confirmed cases Harris Lynch and O Hare[1-9] listed as significant symptoms and signs fever (80 per cent), leukopenia up to 5 400 (70 per cent) renal manifestations like albuminuria (64 per cent) abdominal pain (27 per cent) cylindruria (46 per cent) hyper tension (64 per cent) edema (52 per cent mostly of cardiac distribution) loss of weight hematuria and neuritis Thoracic pain dyspnea headache and vertigo are common The diagnosis is usually made post mortem However with better knowledge of the dermadromes and greater number of biopsies the disease is being recognized more frequently during life [1 0 121 12]

The *cause* of the disease is not known but it has nothing to do with syphilis as was early suggested It is striking that periarteritis nodosa has so often de veloped shortly after or even in immediate connection with various infectious diseases especially those caused by hemolytic streptococci While the staphy lococcus the meningococcus and the gonococcus are on the list of bacteria which have been found in close association with periarteritis nodosa [1 5] the streptococcus is by far the most frequent one A correlation to rheumatic fever with Aschoff bodies and verrucous endocarditis was discovered in four of Spiegel s[1 5] seventeen cases and in one of Rothstein and Welt [133] The clinical course often suggests speticemia The coincidence with well established allergic states and also ex perimental evidence of infection[134] suggests allergy as an important pathogenic factor in periarteritis nodosa [135]

The *treatment* is symptomatic In one case sulfapyridine together with acetylcholine seemed to be curative [1]

Dermadromes—Cutaneous manifestations occur in about 25 per cent [1 0 123] In rare instances almost exclusive involvement of the skin without participation of the internal organs has been observed [124 1 5] The case material permits a tentative grouping[1 4 1 6] into nodular erythematous and hemorrhagic eruptions

The most characteristic element is the periarteritic *nodule* which may be found in or under the skin These nodules have been noted in roughly 25 per cent of the cases but they probably often have escaped observation The lesion is very seldom larger than a pea more often smaller In hemorrhagic cases the nodules may reach the size of a robin s egg[127] or larger and may become cystic and blood filled The nodules which have been seen to appear in crops in various stages of the disease are hardly ever more than fifty in number In order of frequency they have been observed on the forearm chest legs abdomen

[131] Vining G W Periarteritis Nodosa Arch Dis Childhood 13 31 44 1938

[132] Legros J Pe iarteritis Nodosa or Kussmaul Maier Disease First Case Diagnosed in Infant During Life Recovery From Therapy With Sulfapyridine and Acetylcholine Arch. Francaises de Pédiat Paris 2 11? 115 1944 1945

[133] Ketron I W and Bernstein J C Cutaneous Manifestations of Periarteritis Nodosa, Arch. De mat & Syph 40 9 9 944 1939

[134] Matras A Zur kutanen Form der Periarteritis nodosa Wien klin. Wchnschr 51 991 193[illegible]

[135] Spiegel R Periart ritis Nodosa Arch Int Med 58 993 1936

[136] Boyd L J P riarteritis Nodosa Cutaneous Symptoms Bull New York M Coll Flowe[illegible] & Fifth Ave Ho ps 3 175-18 1940

[137] Alkiewicz J Multiple nekrotisierend Periarteritis nodosa der Haut mit [illegible] Arch f Dermat u Syph 168 52 1933

face back fingers scalp scrotum and tongue[1 6] Sometimes a linear reticular or livedo racemosa like arrangement and pulsation indicate their connection with an artery[1 3 128 1 9] This connection can be demonstrated better by capillaroscopy (Weigeldt after Boyd[126]) The lesions are tender even painful and may be slightly raised purplish or red and surrounded by erythematous halos which may coalesce The center may appear grayish and depressed indicating necrotic changes[12] and a scab may appear on superficial nodules The nodular cases may suggest erythema nodosum[1 5] The nodules have a tendency to heal leaving a tan colored pigmentation Matras believes that the nodular type of periarteritis nodosa takes a more benign course

The second important cutaneous feature of the disease is *purpura* Petechiae and small purpuric spots sometimes with a white center[1 5] are common sometimes abundant Large cutaneous extravasations (apoplexia cutanea)[130 131 13] resembling purpura fulminans have been described by many authors[127] These hemorrhages may involve entire regions They may break down and form gangrenous ulcers of varying sizes depth and numbers[1 1 131] sometimes climaxing in the mutilation of the acra of the extremities[121 131] The coagulation time may be prolonged and the fibrinogen reduced to 50 per cent[131]

Besides the most characteristic features the nodules the p gangrene roseola[1] and other erythemas and ephemeral rashes recurring rel tioned Pigmentation though not in the list compiled by Ha tion with rhe O Hare[1 0] is a feature and may have the characteristics of A on the fingers Periarteritic involvement of the adrenals has in fact been ort lived rarely cases (Spiegel after Boyd[126] Edema and profuse sweating night and moderate adenopathy are common symptoms

The *histological* picture is well established It shows infilt walls of small and medium sized arteries with leukocytes and round destructive cells of the Langhans type are common All layers especially the and other thickened and the elastica and the muscle fibers are destroyed[121 1] g to the the proliferation of the intima leads to occlusion thrombosis and he[1 0] Age Tissue and blood eosinophilia are frequently a conspicuous feature T n been cutaneous fat is often the site of a patchy necrosis and of an inflammat ually, filtration with necroses in spots and numerous monocytes and giant ce erize Extravasations are exceedingly common

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[7] Carol W L L and Prakken J R Periarteritis Nodosa Acta d rmat en reol 18 102 1937

[9] Goldschlag F and von Chwalibogowski A L b r inen Fall von Pe iarteritis nodosa mit ausg breit ten Hauterscheinungen Arch f D rmat u Syph 171 622 193

[1 0] Fr un l F Periart riti Nodo a Arch Derr at & Syph 152 1 8 10 0

[131] Löhe H and Ro nfeld H Multiple Hautgangrän b i l eriart riitis nodosa D rmat Ztschr 61 99 3 0 1931

[127] Banowitch M M Tolayes S H and Char t R Periarteritis Nodosa Ann Int Med 16 1149 1179 1912

[12] Poth t in J L and Welt S I riart riti Nodo a Am J Di Chil 1 45 1277 1933

[13] Rich A R and Gregory J F Periart ritis Nodo a a a Manif tation of Hyper n itivity Bull Johns Hopkins Ho p 72 6 1943

[128] Mo che itz F I eri rt riti Nodo a J Mt S ai Ho p 5 337 339 1938

Scarlet Fever

Scarlet fever is caused by certain strains of hemolytic streptococci which are found mainly in the discharges of the upper respiratory tract Contagion occurs predominantly among children from 1 to 5 years of age (rarely in infants) by close contact with patients and possibly though seldom through carriers or media such as milk toys or pets The disease is most contagious during the first week The incubation period is probably two days[136] but the observations vary from one to seven or more days The onset is sudden with nausea and high temperature A few convulsions and vomiting are common at this time but chills are uncommon There are regularly early sore throat and a coated tongue The scarlet fever exanthem appears after twelve to twenty four hours and reaches its height within five days the patient frequently being very ill The fever gradually falls the rash fades and peels within three weeks and then recovery is reached unless complications develop These complications include otitis media (14 per cent) arthritis (7 per cent) nephritis (4 per cent) and a number of rarer conditions (Hunt after Dick[135])

The mortality[137] in the United States is between 1 and 2 per cent in ome communities much less this rate varies considerably during epidemics and in different countries However approximately 4 000 deaths from scarlet fever occur every year in the United States Except for the complications the post mortem findings are es entially negative The diagnosis rests on the clinical picture especially the rash in connection with exposure an epidemic and the occurrence of hemolytic streptococci

Dermadromes —In rare cases the outbreak of the disease may be preceded a transitory diffuse or spotted rash on the inner thighs [138] Such *fore exanthems* cur in other exanthematic infections too Most of the new monographs on arlet fever do not mention this rash

The scarlet fever *exanthem* appears early often during the first day of the ease but occasionally the rash is delayed as much as five days [137] Diffuse ythema of the palate with red spots[136] marks the appearance of the exanthem This exanthem is quickly followed by the skin eruption which starting at the eck creeps downward and reaches the feet in two to three days The face usually remains free but it is flushed from fever Morawetz[139] mentions that the exanthem involves the face The area around the mouth stays pale with a yellow hue This diffuse and relatively wide circumoral pallor includes the lips and often the chin It is much wider and less sharply limited than the narrow perioral strip which often remains unaffected in various other inflammations and pigmentations about the mouth The rash is often particularly pronounced on the femoral triangles on the abdomen and in the bends of the joints Here the folds may appear more marked and slightly hemorrhagic (Pastia s lines)

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[135] Dick C F and Dick G H Scarlet Fever Chicago 1938 The Year Book Publishers Inc

[137] Toomey J A Sca let Fever In J Br nn mann s Practice of Pediatrics Hagerstown Md 1944 W F Prior Company Inc

[138] Schlossmann A nd Hottinger A Sca l t Fever in Pfaundler and Schlos mann Th Di eases of Child n Vol III Philadelphia 193 J B Lippincott Company pp 76-160

[139] Morawetz C Acut Exanth me Scharlach Handb d H u Gk 28 419-4 4 1930

The rash is a bright red erythema in which small punctate splashes can be discerned On the extremities the pin point spots are less numerous and therefore better recognizable These very small points are engorged papillae[136] and follicles[139 140 143] The swelling of the follicles and a slight infiltration of many of the red points may give a chagreen like impression to the hand Mottling of the skin may be present on the extremities[144] In unusual instances the skin is edematous making the rash look like dermatitis Minute clear rarely pustular[145] vesicles may be scattered over the red background This phenomenon which is evidence of a more severe inflammation is known as *miliaria scarlatinosa* The vesicles the content of



Fig 13 —Scarlet fever Rash flushed face and circumoral pallor on third day (Courtesy Dr Max Fox)

which is alkaline do not correspond to the sweat glands They may be abundant or even confluent forming large bullae[138] The erythema fades on transient pressure or when the skin is stroked with the fingernail and after ten to twenty seconds a white sometimes slightly icteric dermographism appears[139] Small numbers of *petechiae* are common especially in the flexures The tourniquet test is usually positive and petechiae can easily be provoked by pinching Edema of the dermis often causes slight puffiness of the face ears and fingers The

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[140] Unna P G Histopathologie d Hautkrankh iten Berlin 1894 A Hirschwald

[141] Kritch N Pachine A and Sidorow I La peau dans la scarlatine Étude histologique Arch de Méd d enf **32** 313 326 19 9

[142] von Bormann F Scarlet Fever Review of Literature Med Klin **37** 661 664 1941

[143] Lehmann W Streptokokkenerkrankungen Erg bn d inn Med u Kinderh **40** 604 740 1931

[144] Sobel N in Mackee G M and Cipollaro A C Skin Dis a es in Childr n New York 1946 Paul B Hoeber Inc

[145] Liebmann C Miliaria scarlatino a suppurativa Med Klin **33** 1368 1937

exanthem reaches its full height during the second half of the first week It then disappears often in the same order in which it came During the period of involution the redness may still be pronounced in the evening although the skin appears pale in the morning During the second week the skin becomes dry and the *desquamation* starts usually about the neck or on the lips sometimes at the sides of the face showing that in these cases the scarlet exanthem had involved the face also The desquamation is at first branny, but in the third week the typical peeling in large flakes develops The thick horny layers of the epidermis of the hands and feet are the last to go The desquamation varies according to the intensity of the exanthem While desquamation of fairly large shreds from the finger tips and toes is common the shedding of glovelike casts is quite rare The epidermis which is ready to peel usually starts to crack under the toes and then peels off toward the tips as well as toward the soles After a few days ragged flakes hang around the nails which in rare instances may come off also It has often been said that the stripping of the shreds proximally from the nails over the digits is an almost diagnostic sign of preceding scarlet fever



Fig 14 —S a let fever Des quamation

Usually the exanthem does not itch However the period of desquamation may be troubled by pruritus Some cases of scarlet fever with a mild exanthem but unusually severe pruritus have been reported [146] In rare cases the rash may fail to develop or may be very light The e cases are contagious and desquamation may or may not follow

In true relapses of scarlet fever the exanthem may repeat itself[138 147] however true relapses are exceedingly rare *Desquamation erythema* [148] or erythema post

146 Lortat Jacob L Le prurit dans la scarlatin La forme prurigin use de la scarlatine Presse méd 1 07 768 19 9

147 Hubenstack Eberhard Zu Klinik der Spätexantheme nach Scharlach Monatschr f Kinderh. 89 1 17 1933

148 Leiner Ca l Hautve änd rung n bei inneren Erkrankungen des Kind salters Wien med Wchnschr 79 1139 1929

scarlatinosum is a dermatosis which is seen in less than 1 per cent [147] during the desquamation period or during relapses. In one type there are round or polygonal red slightly papular spots of fingernail size or smaller which have an accentuated deep red margin and a collar of scales. They cover the lower trunk, the buttocks and the thighs in a much less regular or pronounced pattern than the exanthem [138]. Another variety is a cracked net shaped erythema and dermatitis with desquamation [147].

Striae cutis distensae are not infrequently seen in adolescent girls after scarlet fever (see striae in chapters on puberty and pregnancy).

Moderate swelling of the superficial *lymphatic nodes* is common during the eruption. The nodes under the angles of the jaws which correspond to the tonsils are often infected. These and other neck nodes, rarely other lymphatic glands, may suppurate and break down.

The *oral* manifestations of scarlet fever are of great importance [149]. In the initial stage before the exanthem the pharynx is reddened and the tongue coated. The diffuse initial redness of the throat soon changes into the enanthem which consists of bright red or hemorrhagic points especially over the soft palate and the anterior pillars. The uvula and the hard palate are often left free and relatively pale. The tonsils become swollen early, white exudate showing in the lacunae. The exudate may form diphtheroid membranes and necroses which may cover the entire tonsil. Ulceronecrotic lesions may even invade the tongue[150] and extend to the pillars and the soft palate.

The changing and characteristic appearance of the *tongue* has for more than a century been considered of great diagnostic importance but recently it has lost some of its import since typical scarlatinal glossitis occurs in only one half of the cases and may also be found in measles and German measles [144]. The first changes in the tongue often precede the exanthem in scarlet fever [151]. The early yellowish coating is soon pierced by the swollen red papillae fungiforms producing the strawberry tongue. The edges and the tip of the tongue usually become free early so that a red V shaped area results.

After about two days the yellow coating vanishes. On the fifth to eighth day the whole tongue is deep red and covered with raised papillae constituting the raspberry tongue [138].

Since the first description by Lister in 1858 (Klan[152]) a great number of cases of acute symmetric *gangrene* of the skin in scarlet fever have become known, sometimes under names such as gangrenous purpura, purpura fulminans, or disseminated skin gangrene.

Suddenly, sometimes after a mild or moderately severe course of scarlet fever, usually in or shortly after the third week but occasionally as late as nine months after the onset [153], patches of gangrene may appear on the skin, often in a

[149] Trask, J. D.: Scarlet Fever, Chap. XXI, New York, 1940, Oxford University Press.
[150] Berger, J.: Ulceronekrotische Glossitis bei Scharlach, Monatschr. f. Kinderh. 38: 89, 1938.
[151] Cojan, N.: L'état de la langue dans la scarlatine au moment de l'éruption, J. de méd. de Paris 40: 293-294, 1921.
[152] Klan, H.: Akute symmetrische Hautgangrän bei Scharlach, Klin. Wchnschr. 18: 1538, 1937.
[153] Dick, G. F., Miller, F. M., and Edmondson, H.: Gangrene in Scarlet Fever, Am. J. Dis. Child. 47: 374, 1934.



Fig 15



Fig 16

Fig 15 —Scarlet fever tongue on third day Coating is pierced by swollen papillae fungiformes Strawberry tongue (Courtesy Dr Max Fox)

Fig 16 —Scarlet fever fourth to fifth day Tongue is swollen desquamated along the edges (Courtesy Dr Max Fox)

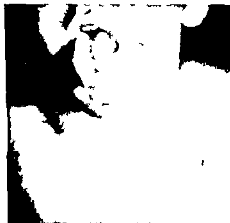


Fig 17



Fig 18

Fig 17 —Scarlet fever fifth day Tongue is clean on anterior dorsum and along the edges still coated on the area facing the soft palate (Courtesy Dr Max Fox)

Fig 18 —Scarlet fever between fifth and eighth day Tongue is red studded with swollen papilla Raspberry tongue (Courtesy Dr Max Fox)

symmetrical distribution. They occur most frequently on the legs, the buttocks and the genitalia[154] occasionally on the arms, hands, face and chest.[155] They range in size from small patches to that of a whole region such as an entire foot or hand. The involved skin undergoes the well known sequence of changes of gangrene: pain, erythema, dark discoloration, blistering and finally demarca-





Fig 19 Fig 20

Fig. 19.—Patch of gangrene after scarlet fever. Ecthyma gangrenosum. (Courtesy Dr. Max Fox.)
Fig. 20.—Foot gangrene after scarlet fever. (Courtesy Dr. Max Fox.)

tion and slough. The hemorrhagic discoloration is not evidence of a hemorrhagic diathesis. The healing tendency is often surprising. The outcome depends upon the size of the lesions, the necessity for amputation and the presence of other complications. The mortality is probably lower than 50 per cent.[15]

[154] Huber, H. C.: Ein Beitrag zur Genitalgangrän bei Erysipel im frühen Kindesalter, Kinderärztl. Praxis 8: 5-11, 1937.

[155] Sw itz, S. F.: Multiple Gangrene of the Skin Following Scarlet Fever, Arch. Dermat. & Syph. 27: 1019, 1933.

The cause of this multiple symmetric gangrene is still little understood Purpura capillary thrombosis and thrombophlebitis[156] have in several instances been shown not to be causative Purpura has occasionally been present [157 158] The findings in amputated limbs failed to demonstrate arterial block [15 153] and the findings of phlebitis were more suggestive of a sequel than of a cause Possibly the explanation may be found in allergic phenomena Gangrene has often been observed during the third or fourth week the typical time of post scarlatinal nephritis and has actually been seen together with it

Another rare complication of scarlet fever is *thrombophlebitis migrans* This is an acute febrile phlebitis usually involving the veins of both legs [156 160]

Circumscribed edema is another rare sequel of scarlet fever [161] It has been known for a long time but it is apparently seen only in some epidemics Steinbrinck[16] reported forty cases of edema of the upper lids in a recent epidemic The swelling was in some instances so severe that it suggested subluxation of the eyeball Involvement of the paranasal sinuses probably plays a part All the skin changes discussed under the heading of septicemia may be observed occasionally

Purpura though relatively rare in scarlet fever may occur just as in the course of other infections It has been seen most often during the third week The platelet count may be normal[163] or low The mortality is high [164] Hemorrhagic tendencies can be demonstrated early

The *tourniquet test* is commonly positive in scarlet fever in fact it had been devised first as a diagnostic procedure in scarlet fever [165] Lately the capillary resistance has been investigated by E E Brown [166] with the more exact Dalldorf[167] suction method It can be shown that the capillary resistance as expressed by the number of petechiae provoked under certain conditions is low at the onset and increases as the patient recovers Age of the patient [168] toxemia and marked desquamation may lower the resistance [166] Myrgard[168] saw wavelike recurrences of lowered resistance in intervals of about two weeks He[168] demonstrated that

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[156] Hueneken F J and Silperstein D M Post scarlatinal Phlebitis Am J Dis Child 26 447 19 3

[157] Box Ch R and Massingham R Purpura Haemorrhagica Complicating Scarlet Fever Lancet 1 295-96 1931

[158] Sundt Odd Purpura mit ausgebreiteter Hautnekrose bei leichter Scarlatina Norsk Mag f Laeg vidensk 92 14 16 1931

[159] Urbach Erich and Gottlieb Philip M Allergy New York 1943 Grune & Stratton Inc

[160] Bates J V Postscarlatinal Thrombophlebitis Migrans Brit M J 1 665 1943

[161] Zischinsky H Eine ungewöhnliche Form von Gefässchädigung beim Scharlach München med Wchnschr 84 1060 1936

[162] Steinbrinck W Unusual Complication (Scarlet Fever) Deutsche med Wchnschr 68 1 1149 0 1942

[163] Fox M J and Enzer N Consideration of Phenomenon of Purpura Following Scarlet Fever Am J M Sc 196 3 1 1938

[164] Wood Smith F G Purpura as a Complication of Scarlet Fever Brit J Child Dis 28 273 81 1931

[165] Leede C Tourniquet Test in Scarlet Fever Münch med Wchnschr 58 293 1911

[166] Brown E E Scarlet Fever—Capillary Resistance Arch Pediat 57 553 63 1940

[167] Dalldorf G A Criterion of Hemorrhagic Diathesis in Experimental Scurvy J Exper Med 53 289 1931

[168] Myrgård A Capillary Resistance and Wheal Test in Scarlet Fever Upsala läkaref förh 37 417-430 1932 Zbl 44 197

Fig 21



Fig

Fig 1 —Sev e purpura after scarlet fever (Courtesy Dr Max I ɔx)
Fig —S vere purpura after scarlet fever (Courte y Dr Ma Fo)

the absorption time of a saline wheal (McClure Aldrich test[169]) is shortened especially in the beginning and in toxic cases

Capillaroscopy shows even in the early period the capillaries to be lengthened and engorged on the arterial side The subpapillary plexus is hyperemic and plainly visible on a brownish background The arterial flushing yields later to a status with both sections of the capillaries about equally filled with cyanotic blood It is more than five weeks until the capillaries appear bright red again on a rosy background with sharply outlined margin and a hardly discernible subpapillary plexus [170]



Fig 3—Purpura after scarl t feve (Courtesy Dr Max Fo)

The *Dick test* for susceptibility to scarlet fever is based on the neutralization of scarlet fever toxin in the skin of the person tested Exactly 0 1 c c of the test solution is injected intracutaneously [136] The test is considered positive if after twenty to twenty four hours an erythema however slight of not less than 10 mm in any diameter is present The reading should be done in bright light Induration is not required and may even be absent in strongly positive reactions A positive reaction shows that the per on is susceptible to scarlet fever The test is usually negative in the newborn infants of immune mothers but becomes positive during the first year of life

[169] McClure W B and Aldrich C A Time R qui d for Disappearance of Intradermally Injected Salt Solution J A M A 81 293 94 1923

[170] Müller Otfried Zur Beobachtung d s Capilla kr i lauf beim M en ch n V handl d deut ch Kong f innere Med 32 11 20 19 1

The newborn infant of a nonimmune mother usually reacts positively In later life the reaction depends on the degree of exposure and silent immunization In a group of children who grow up in crowded conditions for example in an



Fig 24 —Positive tourniquet test (Leede-Rumpel sign) in scarlet fever (Courtesy Dr Max Fox)

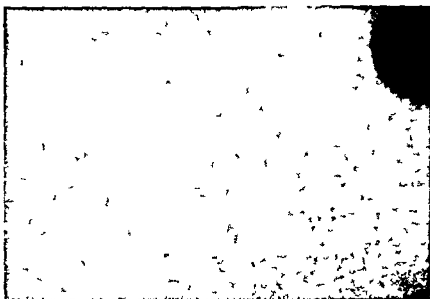


Fig 25 —Positive blanching test in scarlet fever (Courtesy Dr Max Fox)

institution the incidence of susceptibility may be as low as 10 per cent and in rural groups with few contacts it may be as high as 85 per cent [136] The morbidity among children in Milwaukee with negative reactions to the Dick test was found to be only about one fourteenth of the general morbidity (Cummings after von Bormann[171]) Convalescents of scarlet fever have negative Dick tests

[171] von Bormann F Scharlach Monatschr f Kinderh 83 213 261 1940

In rare instances a mild miniature scarlet fever may follow the Dick test [17]

The *blanching or Schultz Charlton test*[173] (Ausloschphanomen) is based on the local blanching of the scarlet fever exanthem by an intracutaneous injection of normal serum serum of convalescent scarlet fever patients or serum of diluted antitoxin in amounts of 0 1 to 0 5 c c A positive reaction consists of blanching of the rash eighteen to twenty four hours after the injection in a zone surrounding the central red spot where the injection was made [136] The positive Schultz Charlton test[173] supports the diagnosis of scarlet fever The area of skin which has been blanched does not peel [174]

There is still controversy about the limitations of these two tests [175 176]

Pathology —There is edema hyperemia and inflammatory infiltration especially around the follicles and sweat glands Endothelium covered fibrous exudates have been seen in the walls of small veins in scarlet fever as well as in other pyogenic infections [177] especially subacute bacterial endocarditis Para keratosis precedes the peeling [141]

It is remarkable that hemolytic streptococci are common in the superficial scales of the peeling skin but could rarely be found in the deeper layers [178] This may mean that the scales become infected from without and that the living skin during the desquamation is no longer infected Recently streptococci have been demonstrated in the endothelial cells of blood and lymphatic capillaries and in adjacent cells [179] The desquamated skin is not considered contagious [144]

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[172] Wallis H R E Miniatu e Scarlet F ver After Dick T st Lancet 2 19 194

[173] Schult W and Charlton W Se ologische Beobachtungen am Scha lachexanthem Ztschr f Kinderh **17** 328 333 1918

[174] Fanconi C Beiträge zum Scharlachproblem Abhandlungen aus der I inderheilkunde und ihren Grenzgebieten N 13 B rlin 1926 S Ka ger

[175] Reisman H A and Be kow A Dick Te t Arch P diat **58** 286 93 1941

[176] Press E and Litvak A M Schultz Charlton and Dick Tests in Scarl t Feve Arch P diat **58** 194-197 1941

[177] Siegmund H Gefässwandreakt on n Ve handl d deut ch path Gesell ch **20** 261 19 5

[178] Kanev kaya M J Pres nce of St eptococci in Scales of Scarlet Fever Pati nts J A M A **89** 1011 19 7

[179] Tornack J H Etiology and Pathog ne is f Scarlet Fev r Hi tologically Demonstrated Storage of Coccus-like Structures in Endoth lial C lls of Skin Mucuou M embrane and Lymph Nodes Klin Wchnschr **21** 581 194

CHAPTER III

SYSTEMIC INFECTIONS

Lobar Pneumonia

In none of the various types of lobar pneumonia are skin manifestations important with the exception of *herpes simplex* (herpes febrilis herpes symptomaticus) which occurs in a high percentage between the second and fifth day usually on the lips The eruption appears as groups of clear vesicles on a red slightly edematous base After one to two days the vesicles become pustular often confluent and finally they dry up The crusts come off after about five days usually without leaving a scar The incidence of herpes varies according to the type of pneumococcus Among 500 cases of lobar pneumonia of all types 30 per cent were herpetic [180] This incidence was observed in London England The herpes incidence among 500 cases in New York was only 12 per cent [181] while many older mostly German figures run as high as 40 or even 50 per cent J A Montgomery[180] analyzed the occurrence of herpes in 500 cases of lobar pneumonia with regard to *types of pneumococci* While the incidence of herpes is about the same (30 per cent) in all types the mortality in the herpetic is lower than in the nonherpetic cases especially in type I in which the mortality is less than one sixth of that of the nonherpetic of the same group The relatively favorable prognosis of herpetic pneumonia has been well established[182 183 184] for a long time Montgomery[180] records a mortality of 14 per cent in the herpetic group and 16 per cent in the total Schwartz s[181] corresponding figures are 5 and 25 per cent which is closer to the old figures [18]

Herpes is uncommon in acute Friedlander pneumonia which has a high mortality (75 per cent) [185]

Petechiae occur in severe cases of pneumococcic sepsis E Fraenkel[186] examined such lesions in two fatal cases Clinically they seemed to be only petechiae the histological structure suggested bacillary metastases but no *pneumococci could be found E Fraenkel[186] emphasizes the rarity of skin manifestations* in pneumococcic infections He believes that the skin enjoys a certain immunity to pneumococci since skin metastases are lacking even when specific metastases are found in many other organs

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[180] Montgomery J A Herp F brill in Loba Pneumonia Lancet 1 1041 1042 1939

[181] Schwartz J Pneumonia 500 Cases M Rec 147 19_ 200 1938

[182] Schönfeld W Di klinische Bed utung d Herp s impl x fü and re Krankheiten und physiologische Zustände Tung Cbl med Monat chr 12 _06-30_ 1937

[183] Na g li O Herpes Simpl x München m d Wchn chr 83 330-344 1936

[184] Goodall F Life Story of Simple Herpes Lancet 1 906 1939

[185] Solomon S Chronic Friedländ r Infection of the Lung J A M A 115 15 7 1536 1940

[186] Fra nkel E M ta tatische D rmato en b i akut r bakt ri ll r Allgemein rkrankung Ztschr f Hyg u. Infectionskrankh 76 153 1914

Equally rare are diffuse or maculovesicular *erythemas*[187 188] A few times pneumococci have been found in the skin lesions The rare varicella resembling rashes may be generalized herpes[189]

As long as the fever is high the skin remains hot and dry It is an old observation that the *cheek on the side of the involved lung is redder* than the other The most plausible explanation is that the patient often lies on the involved side in order to keep this painful side quiet but this explanation is not always correct[187] Only during and after the crisis do profuse sweats occur especially in juveniles These sweats are sometimes followed by miliaria rubra

Systemic Pyocyaneus Infection

In spite of the common infection of wounds with *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*) and of the frequent saprophytism of this microorganism systemic infection is rare and occurs usually in debilitated per ons[190 191 19] Almost all organs may become infected the skin often being involved The skin manifestations of severe pyocyaneus sepsis do not differ from those of other pyemids However there is a characteristic dermatosis *ecthyma gangraenosum* which is known to occur in the wake of measles and various other infections and cachectic states (ee Fig 19) especially in children and which in a consider able number of instances has been shown to be caused by *Pseudomonas aeruginosa* Its character as a skin manifestation of a generalized infection is shown by many analogous autopsy findings in internal organs[190] The skin lesions start as papules but soon become bullous and hemorrhagic and form round sharply outlined necrotic and painful ulcers which may reach the ub cutaneous tissues and even invade the muscles Petechiae and large ecchymo es are supposed to be characteristic[65] Their number varies from one lesion to exanthematic dissemination Healing has seldom been observed since most of these patients die within a short time The general course is that of a septic toxemia[190]

The histologic examination shows many gram negative bacilli in the outer layer of the blood vessels especially of the arteries[185] Atypical apparently hematogenous skin infections with pyocyaneus have occasionally been de scribed[190 193]

Meningococcic Meningitis (Cerebrospinal Fever)

After an incubation period of a few days the onset is usually sudden with high fever severe headache and vomiting Meningitic symptoms ap

[187] Howard C P and Mills E S Pn umonia Oxford Monographs Vol X N w York 1939 Oxf rd University Press

[188] Schmidt LaBaume F and Otto C Zur Klinik Hi t logie und Pathogenese der Pn u mokokken xanth m Arch f Dermat u Syph 169 431-435 1933

[189] Sharp Wm S Eruption R mbli g Va icella in Lob r Pn umonia Brit M J 1 14 192?

[190] Bruck C Di Pyocyaneu rkrankungen derHaut Handb d H u Gk 9 1 125-144 19 8

[191] Klin B S and Vachh A S Th Fatal Cases of Bacillus Pyocy n u Inf ction J A M A 98 528 532 1932

[192] Lewandow ky F Ule rös Haut ff ktion b i Erwachs n n v rursacht durch d Bacillus pyocyaneus Münch n med Wchn chr 1907 II ? 5

[193] Frei W and Wi n r K Ein Fall von ulc rö r Haut rkrankung au der Gruppe des Ecthyma gangränosum (mit Pyocyan usb fund) Arch f Dermat u Syph 134 106 118 19_1

pear after from two to four days There is irregularity of the pulse and respiration painful stiffness of the muscles abolition of superficial abdominal reflexes insomnia and restlessness The patient lies on his side with the knees drawn up The leukocytosis may be very high

After the first week the patient s restlessness often changes to stupor The recovery is gradual the course is varying death may occur in any stage

Before the advent of the sulfonamides the mortality rate was as high as *49 per cent in children under the age of one year and from 10 to 20 per cent above* this age [194] Today the mortality rate has been lowered to 2 per cent[195] and even less [196]

The sulfonamides and penicillin are the drugs of choice in the treatment of meningococcic infections

Dermadromes —A variety of rashes occur with varying incidence Figures between 91[197] and 100 per cent[198] are available [196]



Fig 96 —Meningococci meningitis Purpuric rash (Courtesy Dr Max Fox)

Of importance is a *purpuric rash* consisting sometimes of only a few petechiae occasionally of very many hemorrhagic spots resembling flea bites or larger The rash often being scanty one should look for purpuric lesions on the chest armpits abdomen thighs buttocks and hips A single petechia of the conjunctiva may

[194] Worster Drought C and Kennedy A M Cerebro-spinal Fever London 1919 A & C Black Ltd

[195] Thomas H M Jr Meningococcic Meningitis and Septicemia J A M A 123 264 272 1943

[196] Hill I W and L ver H S Meningococcic Infection in an Army Camp J A M A 123 9 14 1943

[197] Blackerby P F and Caudill F W Epidemiologic Study of Approximately 400 Cases of Cerebrospinal Meningitis Comparative Value of Antitoxin and Antibacterial Serum South M J 31 161 168 1938

[198] Dickson R C Mckinnon N E Magner D and McGillivray N B Meningococcal Infection Lancet 1941 II 631-634

be the only lesion[196] The purpuric rash may develop exceedingly rapidly almost under the eyes of the observer There is no parallel between the extent of the rash and the severity of the infection[196] as had been thought by many older authors[194] However purpura seems to be of more ominous significance than petechiae[199] and the fulminating purpura of the Waterhouse Friderichsen syndrome is an almost certain omen of a fatal outcome Larger purpuric lesions may become vesicular bullous or ulcerative Petechiae are not restricted to the skin They may appear in the conjunctivae in the oral mucosa and in the serous membranes The great significance of the purpuric rash lies in the fact that the



Fig 27 —Me ingococcic meningitis Papuloh morrhagi a h (Cou tesy Dr Max Jo)

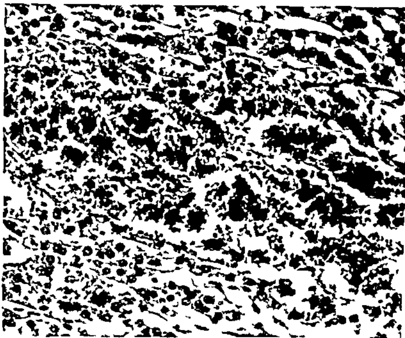
lesions are true *metastatic bacillary lesions* not hemorrhages due to lowered capillary resistance of toxic cause E Fraenkel[67] found meningococci in the cellular infiltrate of the petechial efflorescences He also demonstrated Friedlander bacilli in the purpuric skin lesions of a case of meningitis caused by this microorganism Since then the search for microorganisms in purpuric lesions has become a diagnostic method Tompkins[200] and McLean and Caffey[201] were able to demonstrate diplococci in smears in 80 per cent of their cases To obtain material for the smear a purpuric spot is gently blanched between two fingers and pricked with a fine hypodermic needle Then some serum is squeezed out and

[199] Newcome W and Frame E M Summa y of 50 Cases of C bro pinal Fever U S Nav M Bull 41 960 9 ? 1943

[200] Tompkins V Diagno tic Value of Sm ars From Pu puric Lesions of Skin in Meningococcic Disease J A M A 123 31-3 1943

[201] McLean S and Caffey J End mic Purpu ic M ningococcus Bact re nia in Ea ly Life The Diagn tic Value of Smears From Purpuric Lesio s Am J Di Child 42 10 3 1074 1931

Fig 28



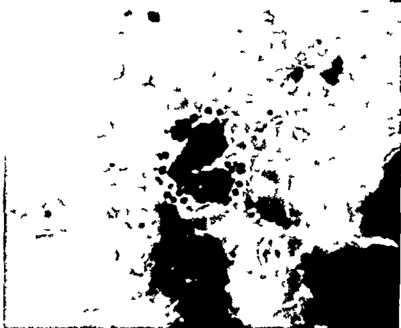


Fig 29

Fig 28 —Fulminating meningococcemia (Waterhouse-Friderichsen syndrome) Engorgement of capillaries in zona fasciculata with early hemorrhagic extravasation (From Pratt Thomas Kelly and Gazes South M J 1945)

Fig 29 —Fulminating meningococcemia (Waterhouse-Friderichsen syndrome) Meningococci in polymorphonuclear leukocyte in smear from purpuric lesion (Crm stal X 000) (From Pratt Thomas Kelly and Gazes South M J 1945)

placed on a slide Quantity is not an object but it is important that the prick be superficial and the exudate not diluted by peripheral blood The smear is stained with Giemsa or Wright stain The smears taken from lesions other than purpuric ones are usually negative

The second type of cutaneous manifestation in meningococcic infection is a *maculopapular rash* which is sometimes seen as early as on the first day of illness It is described as consisting of discrete slightly palpable rather



Fig 30 —Herpes labialis in meningococcic meningitis (Courtesy Dr Max Fo)

scanty (rarely more than a dozen) inconspicuous round well defined pink spots of from 5 to 35 mm in diameter [195, 0] The eruption may coincide with or closely follow the onset or a recurrence of the fever and the general symptoms of the infection [199, 03] The lesions are most often found on the trunk and along the extremities especially about the shoulders They are tender do not appear in crops and vanish within about four days Sometimes they become purpuric in the center and palpable like erythema nodosum Only rarely have they a morbilliform character but they often resemble the rose spots of typhoid fever to such a degree that all other diagnostic factors must be considered in order to avoid errors An early appearance especially on the extremities seems to indicate meningitis rather than typhoid During epidemics this rash alone is considered characteristic enough to establish the diagnosis of meningococcic septicemia

[1 3] Herrick W W Meningococcus Infections Oxford Medicine Vol I New York 1940 Oxford University Press pp 71 106

[03] Priest R 204 Cases of Cerebrospinal Fever J Roy Army M Corps 76 249 60 1941

Several *other types of cutaneous lesions* have been described They include transient rubelliform [204] or scarlatiniform erythematous rashes hemorrhagic vesicles hemorrhagic gangrene [205] and a peculiar urticaria consisting of a large wheal on the buttocks The latter which has been seen by several authors was supposed to be a foreshadowing of a fatal outcome [194] in the pre sulfa era *Herpes* often extensive and in atypical distribution is present in about one third of the cases While often seen on the fourth day it may appear at any time after thirty six hours from the onset [203] *Herpes zoster* involving almost all of the known sites is conspicuously frequent as in lobar pneumonia The vesicles may contain meningococci The belief that herpes is a favorable sign was held by many of the earlier authors however this is not true The opinion was probably caused by the relatively favorable prognosis of herpetic pneumonia

Gonorrhea

Gonorrhea is predominantly a disease of the mucous membranes Cutaneous involvements are rare Ulcerations of the genital skin folliculitis and abscesses or pseudoabscesses are mostly due to exogenous infection of epithelial ducts or follicles from the gonorrheic urethra Hematogenous gonococcic infections of the skin can be grouped under *transitory* urticarial erythematous or hemorrhagic exanthems of the type seen in other bacteremias and *keratotic* eruptions which are characteristic of gonorrhea and hardly known in other diseases

There is a great morphologic variety of exanthems in the former group which makes it difficult to correlate the rash with the gonorrhea by any other evidence than coexistence even after the possibility of an eruption from sandalwood oil, cubebs and similar drugs used in gonorrhea has been ruled out The eruptions which have been described have been seen not only in febrile septic cases but also in relatively mild infections If they repeatedly come and go with exacerbations of the gonorrheic infection the connection is quite obvious The best proof of the specific nature of the questioned eruption is of course the finding of gonococci in the skin lesion This has been accomplished in several cases [206] In one case of septicemia caused by gonococci a macular rash was seen together with arthritis and endocarditis [207] Gonococci could be demonstrated in the blood in the endocardium and in the erythematous spots Kerl [208] saw simple erythema together with epididymitis Scarlatiniform [209] urticarial eruptions with hemorrhagic tendencies occupying the lower legs [210] vesicular [206] vesiculohemorrhagic [211]

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[204] Silverthorne N and Cameron C Meningococcus Infection J Pediat 19 618 6 7 1941

[205] Poinso R Claudo P Auban 1 J and de Balmann A Meningococcemic Gangrenous Purpura Associated With Cerebrospinal Meningitis Cure by Serotherapy Sulfanilamide and Vitamin A Bull et mém Soc méd d hôp de Paris 55 891 896 1939

[206] Margolin E S Gonorrheal Dermatitis as Part of Systemic Gonorrhea Urol & Cutan Rev 47 512 514 1943

[207] Dorner L Gonokokkensepsis München med Wchnschr 70 1069 1923

[208] Kerl W Gonokokkenexanthem Zbl 49 587 1935

[209] Cojan G Sept[i]cémie gonococcique récidivant avec déterminations rar[e]s Rev roum d Urol 3 498 502 1936 Zbl 56 346

[210] Sullivan S J Cutaneous Eruption Accompanying Gonorrhea Case of Hemorrhagic Exanthem Urol & Cutan Rev 38 93 95 1934

[211] Keil H Types of Gonococcal Bacteremia With Characteristic Hemorrhagic Vesiculo-Pustular and Bullous Skin Lesions Quart J Med 7 1 15 1938

hemorrhagic [9, 212, 213] nodular [214] herpetiform [215] erythema exudativum multiforme and erythema nodosum resembling rashes [10, 16, 17] are an illustration of the multiplicity of appearances which these bacteremic eruptions may assume [215] Sometimes these rashes show very distinctly that they are caused by focal infections Sullivan [10] observed an acute eruption of suppurating nodules after dilatation of a urethral stricture



Fig 31 —Keratosis gonorrhoica (From Epstein E Am J Syph 21 148 1937)

In some instances gonococci have been found in purpuric lesions (Bruusgaard and Tjotta after Langer [15]) and in abscesses Icterus is mentioned in several cases [18] In spite of the great morphologic variety these bacteremic gonococcids are rare and do not differ much from the eruptions seen in pyogenic septicemia

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[212] Wiedmann A Beiträg zur Pathologie der Gefässerkrankung der Haut Die gewöhnlichen Veränderungen beim hämorrhagischen Gonokokkenexanthem mit besonderer Berücksichtigung der Gefässveränderungen Dermat Wchnschr 98 541 54 1934

[213] Ladany E and Hughes J D Etiologic Considerations of Keratosis Blennorrhagica Report of Case in Which Penicillin was Used Arch Dermat & Syph 54 150 178 1946

[214] Decastello A and Weltmann O Febris maculosa intermittens (Meningo- und Gonokokkämie Febris intermittens pseudopaludosa Meningokokken Lenta Sepsis) Wien Arch f inn Med 20 4 9-4?? 1930

[15] Langer E Hautkrankheiten bei Gonorrhoe Handb d Haut u Geschlk 20 2 40-74 1930

[215] Feld I Aetiologie des Erythema nodosum Zbl 36 712 1931

[16] Ichikawa T and Ohmori S Beiträg zur Kenntnis des Gonokokkenexanthems Jap J Dermat & Urol 34 511 517 1933 Zbl 48 2 1

[216] Murdock, J G A Case of Keratodermia Blennorrhagicum Brit J Ven Dis 12 242-24? 1936

Of much greater dermatological interest are the rare *hyperkeratoses* in gonorrhea keratoderma blennorrhagicum (keratosis blennorrhagica) Only 166 cases have been described since Vidal s [19] first observations in 1893 It has been estimated that keratosis blennorrhagica occurs about once in 5 500 cases of gonorrhea [23] These dermatoses form a clinical picture which is almost exclusively connected with gonorrhea and it certainly is one of the most characteristic dermadromes peculiar to any one infection Most of the patients are young men suffering from chronic urethral gonorrhea usually with complications particularly arthritis and ocular complications The gonorrheal infection frequently is of long standing [20] even many years when the rash breaks out The eruption often starts with a papulovesicular exanthem In some cases the primary lesion is described as a small glossy pink papule resembling a droplet of wax The vesicles dry up but instead of peeling as one would expect they transform into pseudopustular lesions which look yellow but do not contain pus These become keratoses and finally form a large hobnail shaped conical lesion of layer texture The keratoses are rupioid limpet shaped and have a flat or umbilicated top with a yellow center which contains brittle white horny detritus The bottom layer of horny material forms a yellow clifflike ring around the lesion which is sometimes surrounded by an inflammatory areola The keratotic top is easy to remove leaving a shallow pink slightly moist or gelatinous [21] erosion Keratoses at these areas are often of follicular origin The lesions may grow slowly from pinhead size to several centimeters in diameter and they may coalesce into large rough hyperkeratotic plaques mostly on the soles and around the big joints particularly if the joints are inflamed In these plaques many pseudopustular cavities may be found The extremities are in some cases studded with button or medallion shaped lesions which may reach 1 cm in thickness The *penis* is a site of predilection for the gonorrheic dermadromes [22] which may appear as typical keratotic papules On the glans and on the inner surface of the foreskin they may appear as glossy red flat papules or macules [23] which may coalesce into polycyclic patches Sometimes the keratotic character of these lesions is marked by a grayish macerated crumbling horny top layer (balanitis circinata) The keratoderma may even be restricted to such penile eruptions These lesions occasionally resemble a syphilitic chancre (Tullien after Langer [15]) or lichen planus

The *scalp* sometimes becomes involved [24] The *nails* [25] [26] often become thick dull and brittle and subungual keratoses may raise or loosen the nail The

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[19] Vidal E Éruption généralisée de croûtes cornées avec chute des ongles Ann d dermat et syph 4 3 1893

[20] Stromingr L Quelque considération sur la kérato blennorragique J d urol 31 251 257 1931

[21] Scholtz M Gonorrhoal Keratoderma Arch Dermat & Syph 21 961 969 1930

[22] Arning and Meyer D lius Con Hyperkeratos Balaniti circinata gonorrhoica b trabl t r Vorhaut Arch f Dermat u Syph 108 3 26 1911

[23] Sherman W L Blumenthal F and Heidenreich J Blennorrhagic Balanitiform Keratoderma Arch Dermat & Syph 39 422 429 1939

[24] Frühwald Keratosis blennorrhagica Zbl 51 253 1935

[25] Cederberg A Abortivformen der gonorrhoischen Keratodermien Acta dermat venereol 13 43 2 193

[26] Cornbleet T and Pace F R Keratoderma Blennorrhagicum Arch Dermat & Syph 30 91 1934

whole nail bed even the entire tips of the fingers or toes may be covered with the keratotic masses In several instances sharply contoured round or polycyclic irregular grayish patches with erythematous borders have been observed on the palate and on the buccal *mucosa* [223, 27, 9, 9]

The general *distribution* of the rash is largely symmetrical All *degrees* of involvement from a single keratotic patch on the penis [4] to universal erythroderma have been seen Naturally the discomfort and suffering of the patient depends on the extent and the degree of tenderness of the individual lesions The appearance of new crops is usually coupled with renewed arthritic attacks The eruption may last months or years depending mainly on the course of the gonorrhea but also on the degree of involvement of the skin The majority of the cases of keratosis blennorrhagica finally heal but about 10 per cent fatalities have been recorded [213, 1]

The *histological* picture is characterized by heavy keratosis and parakeratosis with formation of cavities There are edema and cellular infiltration in the papillary stratum

Gonococci have been found in typical lesions in at least seventeen instances [13, 9, 30] although much more often the efforts to find the microorganisms have been in vain The positive findings are definite proof of the hematogenous infectious nature of the eruptions which already had been suggested by the clinical relationship to arthritis endogenous conjunctivitis and iritis and the symmetric and follicular distribution on the extremities Occasional observations give further support to the conception of a focal infection Scholtz [1] saw a flare up of the joint symptoms and the appearance of a new crop of heavily crusted lesions after 8 c c of gonorrheal vaccine (instead of 0 8 c c) had been administered by mistake Similar reactions have been seen after treatment with vaccine [31] and warnings against vaccine therapy of such hyperergic patients have been voiced [227] The extirpation of the infected seminal vesicles resulted in the healing of a gonorrheic exanthem and the dilatation of a urethral infiltration or other urethral manipulations produced flare ups [3] in at least five instances [13] (Lewin after Langer [15]) These observations are not only evidence that the gonorrheic keratodermas are caused by focal infection but they show the role allergy plays in producing the characteristic clinical entity The scarcity of the gonococcus has its analogy in the paucity of microbes in tuberculids trichophytids and other

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[9] Fr i W Con E nth m d r Mundschleimhaut Balanitis ci c nata g no h ica b i Circumcidie t m Zbl 44 371 1933

[3] Col and Driv K rato lerma Bl nnorrhagica Arch D rmat & Syph 19 836-837 19 9

[229] Barrett C C K ratod rma Bl nnorrgicum two case Gono o cu in Lo al Le on A h Dermat & Syph 22 6 7 636 1930

[31] Comb s F C a d B h man H T U of Vitamin A in I at i Bl nnorrhagi a Arch Dermat & Syph 46 7-8 33 1942

[27] Scomazzoni T Ch atod rmia bl n rragica Clo ital di d rmat If 1 36-36 1931 Zbl 39 369

[232] Mathieu H Uréthrites à gon c qu récidiv ntes arthropathie multiples t ubl troj hiques J d mal cutan et syph 1900 Ca mé t N ntes 1900

fluids The complement fixation reaction has several times been found to be positive [33 236]

The provocation of specific lesions by irritation with phenol [37] (not confirmed by Keim[238]), by herpes lesions (Buschke after Langer,[216] Gjessing after Langer[215])



Fig 32 —Keratosis blennorrhagica without gonorrhea (From Lev r W F an l C awfo d G Mar shall Arch Dermat 1944)

by inoculation with gonococcic pus and by maceration with wet dressings [39] demonstrates the changed capacity to react which has developed under the influence of the infection Possibly the bilamitic kerato es are caused by inoculation of gonococcic pus into an allergic skin which has acquired the peculiar keratogenic tendency

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[3] C u) and Jac b K at 1 ma Bl n rrhagicum Arch D rmat & Syph **21** 703 704 1930

[33] Löh H and Ro nf ld H Klinisch und phy iologi ch-ch mi h l nt rsuchungen üb r di Hyperkerat senbil lung bei (onorrh ä und l i I oria l pu tulo a arthropathica D rmat Zt ch **65** 353-374 1923

[35] Be on B B an l Ebert M H K ratod rma Bl nnorrhagicu n Arch D rmat & Syph **31** 739 741 1935

[37] Le s D an l Pe ival (H K rato l rma Blenn rrhagicum Lanc t 193 II 1116-11 8

[39] K tsuji O S ktion befun l der K rat si (norrh ic Jap J D rmat & Urol **32** 98 193 Zbl **43** 92

[238] K im H 1 Hi tog n si of K ratod rma Bl nnorrhagicum Arch D rmat & Syph **9** 493 19 4

[215] Lo an l r W Let r K rato l rmi n im Anschlu an (lenkaff kti n n gonorrhoi chen und nichtg n rrhoisch n Ur r ung Acta l rm n r ol **8** 2 2 4 19 7

The predominance of the male sex in a ratio of 15 3 1 [15] and some autopsy findings seem to support the assumption of endocrine influences [15, 37]

In a small number of clinically typical cases it has not been possible to secure the diagnosis of a gonorrheic infection [15, 40, 41] nor to obtain a suggestive history In the cases with a history of gonorrhea even many years prior to the dermatosis the existence of gonorrhea can hardly be ruled out

Fig 33 —Reiter's disease Lesions are at first flaccid pustules containing macerated epithelial cells later hyperkeratotic (From L W F and Crawford G Marshall Arch Dermat 1944)

Lately several cases of the syndrome arthritis urethritis conjunctivitis and keratoderma have been described in which all efforts to corroborate gonorrheic infection failed [41, 42, 43] These cases belong at least in part to *Reiter's disease* the etiology of which is unknown Penicillin is ineffective

Bos and C nn r c nor h sch Hyp rk rat en ahn Cono rh e Zbl 32 3 1

Le r W F and C wf rd C M I rato s Bl nnorrlagica With ut Gonorrh a R It r s Diseas Arch D mat & Syph 49 389-39 1944

Ferguson A C and I s Frank J K ratod rma Bl nnorrhagica m Furth r Obs rva ti n a to Eti logy Brit J D mat 55 12 1943

Sarg nt J C R it Syndrom J Urol 41 5 8 194

The similarity of gonorrheic keratosis to arthropathic psoriasis may be considerable. However, the history and presence of psoriasis, the vesicular primary lesions, the degree of keratosis, the distribution, the gonorrheic evidence, and a biopsy will secure the diagnosis. In psoriasis the arthritis follows the skin lesions while gonorrheal arthritis is more likely to precede the exanthema.[244] Rupioid or tertiary syphilis may have to be ruled out.



Fig. 34.—Reiter's disease. Keratotic round lesions on glans penis. (Courtesy Dr. Sargent.)

The treatment is to heal the gonorrheic infection. The treatment with vaccines should be undertaken with the greatest caution to prevent exacerbations. Many authors stress the importance of proper nutrition and nursing of these patients who are often extremely weak, uncomfortable, emaciated and anemic. Vitamin A had good effect in one case after sulfathiazole had failed.[239] As local measures salicylic acid in plasters and ointments to remove the excessive keratotic masses should be applied. Great care should be taken to avoid irritation and maceration of normal skin in order to prevent provocation of new keratoses. Penicillin has in the only reported case of its application in keratosis blennorrhagica[245] failed to influence the course. It must be given further trial with high doses and prolonged treatment.

Poliomyelitis

Rashes are not a characteristic of infantile paralysis. Red dermographism (tache cérébrale) is mentioned.[246]

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244 Epstein, E.: Differential Diagnosis of Keratosis Blennorrhagica and Psoriasis Arthropathica, Arch. Dermat. & Syph. 40: 54, 559, 1939.

245 Kapetulsky, F. M.: Keratoderma Blennorrhagicum, Am. J. Syph., Gonor. & Ven. Dis. 29: 361, 1945.

246 Wilson, J. L.: Poliomyelitis, Oxford Medicine, vol. V, New York, 1940, Oxford University Press, pp. 107-124.

Erysipelas

Singer[101] observed various simple polymorphous or purpuric erythemas in the course of 25 per cent of his erysipelas cases No substantial confirmation of this observation has become known

Chancroid

Lennhoff[247] reported a case of erythema nodosum like eruption in a case of ulcus molle The secondary lesions ulcerated contained Ducrey Unna bacilli and were inoculable into the normal skin of the patient Werther[248] succeeded in demonstrating the streptobacillus in the blood in a case of disseminated ulcera mollia Hematogenous infection from a soft chancre seems to be exceedingly rare since hardly any other well corroborated ca es have become known

Typhoid Fever

Typhoid fever is an endemic and epidemic contagious food or water borne disease caused by a gram negative motile bacillus *Eberthella typhi* After an incubation period of from one to two weeks the disease starts insidiously with a slowly rising fever which reaches a high level with small morning remissions during the second week and diminishes by lysis during the third week or later The pulse is much slower than the temperature would lead one to expect

Abdominal and splenic tenderness and diarrhea with pea soup like stools are the most common symptoms Delirium and severe general emaciation are other clinical features at the height of the disease

Complications in almost every organ are known and the severity of the disease varies from symptomless carriers and walking typhoid to fatal cases The outstanding post mortem finding is hyperplasia of Peyer s patches in the small and large bowel The hyperplasia often results in ulceration which may lead to hemorrhage perforation and peritonitis The spleen is enlarged and there is fatty degeneration of the liver

Dermadromes —Typhoid fever has a characteristic exanthem known as *rose spots* or roseola The rash consists of thin almost macular papules which blanch on pressure and measure hardly more than one half centimeter in diam eter They appear in small crops and last about three to five days While the crops come and go about one to two dozen lesions are usually present from the end of the first week of the disease to the second or third week rarely outlasting the fever They almost always disappear without desquamation or pigmenta tion In rare instances the rose spots are papular [49] [50] hemorrhagic or vesicular

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[247] Lennhoff R Uber in n Fall von knotig n v relt roden hämatog nen M tastasen an den Unt rschenk ln b i w i h m Schank r Arch f D rmat u Syph 131 80-86 19 1

[248] W rther Multipl diss mini t Ulce a mollia bei welch n Streptobazillen au d m Blute ge ücht t wurd n Zbl 37 32 1931

[49] D re F Cut n ou Aff cti ns in Va i us Dis ases Brit J Dermat 18 4 0 1906

[50] Ro nthal S I Zur K nntnis seltene Hauteruptionen b i typhösen Erkrankungen De mat Wchnschr 89 981 983 19 9

The eruption is mostly concentrated on the abdomen the chest and the back and it usually appears first on these areas *Only in exceptionally dense* eruptions does it invade the limbs and then the density decreases distally The neck is rarely involved and the face remains free [51] The exanthem is a scanty one compared with those of other infections particularly in small children The number of rose spots seems to vary in epidemics An abundant rash is no indication of the severity of the infection [251 252] While some good observers failed to detect the exanthem in as high as 20 per cent [2 1] other authors (Eichorst after Miller [52]) were able to detect rose spots in all the 2 000 cases of a series

The *pathological* examination of the lesion shows a superficial rather thin, mainly leukocytic perivascular infiltrate in the upper corium which in the rare papular lesions invades the epidermis [67 50 53 54] The lack of plasma cells is striking [50] Typhoid bacilli are in rare instances seen as metastatic deposits in the lymphatic spaces or between the cutis and the epidermis [54] which may become separated within the small area of the rose spots Frequently they can be cultured from the rose spots However with the development of the blood culture this method has lost its diagnostic importance [255]

Hemorrhagic exanthems in typhoid are rare H Curschmann [51] saw only 6 among 2 000 cases (all six patients died) The percentage was higher in other epidemics (McCrae after Miller [5]) Curschmann s[251] observation of a small epidemic of typhoid with purpura is remarkable A mother and six children all showed purpuric rashes While their cases took a favorable course the father developed a hemorrhagic bullous eruption and died [256] Roper [56] saw a similar case with extreme thrombopenia and leukopenia The bullae appeared especially over the bony prominences

Scarlatiniform morbilliform papular [57] varioliform [58] and other rashes may *occur*[85] *(Da Costa after Dore*[249]*)* but they *are rare* The *absence of herpes* is notable Osler[85] saw herpes only 20 times in 1 500 cases Several clinicians feel that the presence of herpes should be a warning against a premature diagnosis of typhoid fever

Miliaria crystallina (sudamina) is supposed to be more common than in other infections The content of the clear vesicles is neutral or slightly acid The blisters dry up and are destroyed before they become pustular Miliaria appears mainly on the abdomen the chest and the thighs not on the face [51] Urticaria is an occasional (0 3 per cent) complication *Furunculosis* and *decubitus*

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[251] Curschmann H Der Unterleib typhus in Nothnagel s Speci ll Pathologie und Therapie vol III Vienna 190? Alfred Hölder pp 108 119

[252] Mill r J L Typhoi l Fever Oxford Medicine vol IV New York 1940 Oxford University Pres pp 666 738

[253] Poehlmann A Unte s an Typhus und Paratyphu roseolen Arch f De mat u Syph 131 381 452 19?1

[254] Fraenkel E Ro eola typh sa und paratyphosa München me l Wchnschr 9 325 3?8 1916

[255] Baerthl in K Abdominal Typhus Koll und Wassermann s Handbuch der pathogenen Mikroorganismen vol III 2 p 1 14 1931

[256] Röper K Bullö e hämorrhagisch D rmatos bei Typhus München m d Wchnschr 2 2030-2037 1931

[257] Trusewitsch B Typhus abdominalis mit atypi chem Exanthem München med Wchnschr 73 2249 ? 50 19 ?

[258] Gottschalk C Varioloartiges Initialexanthem bei Typhus abdominalis München med Wchnschr 72 17 19 5

are common and troublesome Curschmann[51] described a type of bedsore which he often saw as a subcutaneous decubitus Subcutaneous ab cesses devel oped in the pressure areas and later opened forming multiple sinuses Both furunculosis and decubitus can, to a certain extent be prevented by meticulous nursing care Mottled sievelike pigmentation and depigmentation has often been seen on the abdomen of children after typhoid fever [59]

Noma and other buccal ulcerations are very rare complications Other *ulcerations* include ulcus vulvae acutum [60 26] and a imilar vulvar ulceration [61] with raised edges and a necrotic floor

The *tongue* is furred especially at the height of the di ease The edges and the tip are often clean in contrast to the dorsum

The face is flushed in the early period and dull and listless later [85] Osler and Christian[88] emphasize the yellow color of the palms and soles and mention a very distinctive musty odor of the skin The author has been unable to find more exact observations on this odor and in attending many patients with typhoid he has been unable to notice it

Effluvium capillorum is very common after typhoid but only rarely does it reach extreme degrees with complete loss of the hair *Beau s lines* of the nails are usually noticeable but shedding of the nails is rare

The diagnosis of typhoid fever cannot rest upon the roseola alone but it constitutes a most valuable diagnostic criterion For most practical purpo es the paucity of the lesions the complete blanching on pressure the distribution on the trunk and especially the abdomen and the appearance of recurring crops will suffice to distinguish the roseola in typhoid from the rash in spotted typhus and other rickettsial diseases In the rickettsioses the more abundant rash ap pears within two days in one outbreak is usually hemorrhagic and the individual lesion is less neat and regular There is more tendency to involve the extremities especially the more distal parts [51]

A negative Wassermann and lack of other syphilitic manifestations will rule out syphilitic roseola which is usually abundant and has larger individual lesions

Paratyphoid Fever

The clinical picture in paratyphoid fever including the rash resembles typhoid fever The rash was seen in about one half of the cases of an epidemic recently observed in England [63]

The *rose spots* in paratyphoid are more numerous than in typhoid They occasionally cover even the hands and cheeks and desquamation occurs Like the rose spots in typhoid fever the roseolae of paratyphoid are true bacterial

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[59] Henyi Vas. J Hautersch i ung n bei d m infantil n Abd minaltyphus Orvo képzés 21 Hainl s Special I ue 3 4 1934 7bl 81 ? 4

[60] Be lin O U l u vulva acutum in Typhoid F ve Arch Dermat & Syph. 39 89-91 1939

[61] Zann ill P Ulc ra ioni specifich d l g nitali est rni di una ma ata di f bbre tifoid Poli clinico (sez prat) 44 168 1691 1937

[26] Polinso R and Batt ll P Typh id With B ccal Ulcerations and Terminal Hematemesi in Chil 1 5 Years Ol i Mars ill-méd 2 692-698 1939

[63] F a r W M Clove B T J and Class \ Epi i mic of Paratyphoid B Fever in Liverpool and District Brit M J 2 369-371 1937

metastases which contain bacilli sometimes even when the blood culture fails to demonstrate them The pathology of the inflammatory reaction is similar to that of typhoid [264]

Brucellosis (Undulant Fever)

Brucellosis (undulant fever) is a mild septicemia caused by bacteria of the genus Brucella which includes several pathogenic varieties *Brucella melitensis* (Bruce) is found in goats *Brucella abortus* (Bang) in cattle and *Brucella suis* (Traum) in swine The microorganisms are very small pleomorphic gram negative nonmotile bacteria which are pathogenic for guinea pigs The infection from goats is also known as Mediterranean or Malta fever the infection from cattle as Bang s disease

The routes of infection in man are the gastrointestinal tract and the skin The incubation period varies from ten days to three weeks [65] The on et is gradual and the course of the fever varies Most characteristic is the undulant type with repeated periods of persistingly high temperature of ten to twenty days in duration The general condition remains good the paucity of objective signs is a remarkable clinical feature [266, 67]

The disease is rarely fatal but a great number of complications are known They include heart and lung manifestations arthritis neuritis meningitis encephalitis orchitis mastitis abortion and others The laboratory diagnosis is based on agglutination blood cultures which need two weeks to grow and skin tests with brucella vaccines which are more reliable than serum agglutination [268] The cutaneous reactions can be used for differentiation of the various types

Dermadromes —Skin manifestations are either ectogenous or hematogenous The former occur at the site of *contact with infectious material* particularly on the hands and forearms of veterinarians after delivery or manual removal of the placenta of Bang infected cows These persons as a rule do not have a general Bang infection They seem to become silently sensitized by repeated contacts Thirty per cent of 325 Danish veterinarians [69] 10 per cent of the Swiss [70] and 20 per cent of fifty veterinarians from Michigan[271] suffered from this allergy In some cases warmth or itching and urticaria are felt during or very shortly after the contact While this early reaction may be caused by other substances in the cattle serum or placenta [267] a second type of eruption a

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[264] Fra nkel E U ber Ro ola paratypho a Ztschr f Hyg u Inf ktionskr **93** 372 38 1921
[265] Ha dy A V Jordan C F and Bort I H Undulant Fe er Nat Inst Health Bull No 158 pp 89 1931
[266] Robinson F H and Evans A C Ch onic Bruc llosis J A M A **113** 201 206 1939
[267] Huddle on J F Bruc llo i in Man and Animals New Yo k 1943 Commonwealth Fund
[268] Huddleson J F Th Diagn si and Control of Bruc llo is J Oklahoma M A **35** 106 111 1942
[269] Haxthau n H and Thom n A Brucella Au schlag b i Ti rä zten Eine eigentümlich professi n lle Hautaffection wahrscheinlich all rgi cher Natur h rvorg ruf n von Bacillu abortus (Bang) Arch f Dermat & Syph **163** 4 7-491 1931
[270] Schoch A Skin Le ions in Brucell(is P axis **32** 81 591 1943
[271] Huddleson I F and Johnson H W Bruc llo i I The Significance of B uc lla Agglut ins in the Blood of V te inarians J A M A **94** 1905 1907 1930
[271] Jadassohn W Bruc lla Bang Ausschlag und Urticaria bei Tierärzten Zbl **44** 5?0

papulopustular folliculitis which develops within two days is generally considered to be a specific reaction to *Brucella abortus* (Bang) The eruption is described by Huddleson [67] as consisting of small discrete elevated, reddish widely separated follicular papules from 2 to 5 mm in diameter and 1 to 2 mm in elevation The rash itches or burns intensely and may last as long as three or four weeks Occasionally deep necrotic tuberculid like lesions or erythema exudativum multiforme resembling forms are seen Erythema brucellum, as the condition has been termed by Huddleson and Johnson is rarely followed by general brucellosis (Dietel and others after W Jadassohn[27]) In some of the sensitized persons, the attacks seem to become more acute with renewed exposures [73]

The systemic infection infrequently (11 per cent[274]) produces rashes Their incidence seems to differ in various countries * They have been described as macular as resembling the roseola in typhoid [275] (Curschmann after W Jadassohn) as star shaped vividly red or purple spots on the forearms neck and face in porcine cases [277] morbilliform [278] scarlatiniform [79] (Grocco after Lustig and Vernoni) erythema exudativum multiforme like [280] as papular rashes involving cheeks neck and extensor surfaces [281] hemorrhagic bullous varicelliform [283] and as resembling dermatitis herpetiformis and lasting over three years [284] The appearance in crops and the evanescent character of the rash are often emphasized Aphthae in the mouth and a bad taste are sometimes noted early Tonsillitis vesiculosa and uvulitis have been described [285] Ulcus vulvae acutum occurs as a complication as it does in typhoid fever [286]

Gabbi[287] tried to *differentiate* the dermadromes of morbus Bruce (Malta fever) and morbus Bang In the former he found the rash more often scarlatiniform in the latter more frequently vesicular and accompanied by bromidrosis Profuse and exhausting sweats are one of the most unpleasant features of brucellosis [67] Sudamina maceration and desquamation often follow the sweats [288]

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* In Iowa almost no rashes have been observed in a large number of cases (Personal communication to the author from Dr B rtz and Dr Jordan Des Moines Iowa)

273 Gottron H Brucella-Ausschläge bei Tierärzten und Melkern Zbl 58 243 1938

274 Böhmer K Bang Infektion des Menschen Erg hn d Hyg Bakt Immunitätsforsch u exper Therap 12 453 515 1937

275 Kümmerling J Bang Disease in Man Zschr f ärztl Fortbild 35 440-443 1938

276 Löffler W Febris undulans Bang des Menschen Leipzig 1930 Curt Kabitzsch

277 Nagel W Uebertragung der Banginfektion vom Schwein auf den Menschen Schweiz med Wchnschr 61 970-978 1931

278 Rimbaud L Janbon M and Alquié R Undulant Fever—Generalized Morbilliform Erythema in Melitococcosis Arch Soc d sc méd et biol de Montpellier 18 647-648 1937

279 Lustig A and Vernoni G Maltafiebe Kolle Kraus, Uhlenhuth Handbuch der pathogenen Mikroorganismen Berlin 1928 Gustav Fischer and Urban & Schwarzenberg pp 511 575

280 Arakelov C Das Maltafieber in Aserbaidschan Vener 1 6 1368-1376 1938

281 Custer H Bang Infektion des Menschen Schweiz med Wchnschr 1 284 68 1930 Zbl 30 3

282 Nakkawajik W N and Karkadinowsky J A Ueber Banginfektion beim Menschen Deutsche tierärztl Wchnschr 38 369-372 1930 Zbl 35 3 4

283 Zimmermann F Haut und Nervenerscheinungen bei Morbus Bang Cas lek cesk 75 145-147 1936 Zbl 54 4

284 Urbach E Food Infection (Bacillus Bang) Wien klin Wchnschr 42 341-344 1929

285 Hörbst L Diagnosis of Otorhinolaryngologic Conditions due to Undulant Fever Monatsch f Ohrenh 71 1153 1160 1937

286 Katzenellenbogen I Ulcus Vulvae Acutum (Lipschütz) Following Malta Fever Tel Aviv Palestine 1940 Harefuah

287 Gabbi U Morbus Bruce Morbus Bang Clin med 11 208-232 1933 Zbl 46 84

288 Paterson D H and Hardwick C Undulant Fever in Children Arch Dis Childhood 13 65-68 1938

Only few histological examinations of the lesions have been made and they refer to the contact eruptions or to cutaneous reactions with *Brucella melitensis* allergen Perifollicular and perivascular infiltration with lymphocytes leukocytes and monocytes and occasionally an abscess have been observed [7, 273, 289]

Plague

In bubonic plague the primary skin lesion is caused by the bite of an infected rat flea It may remain small and painless or it may develop into a pustule or even into a carbuncle followed by large suppurating bubos and septicemia In the pulmonary form of plague a rapidly fatal septicemia follows or accompanies the severe pneumonia The exciting organism is *Pasteurella pestis* which is found in the blood the sputum the urine and in many lesions especially in the bubonic pus No other bacillus is known to occur in bubos in such large numbers [290]

The disease is prevalent among several rodents Occasional cases or small epidemics have often been seen in the western and southern United States The data on the mortality and the value of serum and other treatment are extremely divergent In many epidemics the mortality was higher than 80 per cent

Dermadromes —Hemorrhagic inflammation is a characteristic feature of the infection This is particularly true of the *plague carbuncle* which otherwise does not differ very much from any other carbuncle The plague carbuncle starts as a small infiltrate with one or several blisters on its surface These blisters may coalesce into a bulla with seropurulent and often hemorrhagic contents in which plague bacilli abound The bleb disappears fast leaving a deep necrotic ulcer with raised edges on top of a rapidly growing cellulitis A lymphangitic streak sometimes with bubonuli connects the carbuncle with the regional lymph nodes which turn into *bubos* The development of the carbuncle may become arrested in any stage leaving hard cutaneous infiltrates which abound in bacilli and are known as *plague boils*

The plague carbuncle is only occasionally the primary lesion of the plague infection More often the carbuncle is a metastatic hematogenous or lymphogenous infection [291] Sometimes the carbuncle develops at the site of infection at a later time than the bubo The incidence of carbuncles varies in the epidemics from 10 to 15 per cent being a fair average [291] Araujo[292] in a recent report found skin manifestations in only 7 per cent Other skin manifestations are erythema pustules vesicles bullae and hemorrhagic lesions The latter are supposed to be so common and their appearance so ominous that from them originated the name of black death as the disease was called during the great European outbreaks in the Middle Ages Such large fulminant hemorrhagic skin lesions have

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[289] Gersh I and Black W C Histology of Cutaneous Reaction to Brucella Melitensis Antigen Arch Path **27** 307 31 1939

[290] Lloyd B J Personal Experiences With Bubonic Plague J Trop Med **44** 119 123 1941

[291] Müller H F and Poch R Die Pest Nothnagels Specielle Pathologie und Therapie Vienna 1900 Alfred Hölder

[292] Araujo F Hauterscheinungen bei Pest Statistisches Klinisches Pathogenetisches Brasil med **25** 1-4 19 1 7bl 4 1.2

not been noticed in the large plague epidemics of modern times However petechial rashes occur which contain bacilli and therefore are a true metastatic infection (Albrecht and Ghon after Muller and Poch [91]) Hemorrhagic streaks around the navel and in other sites have been recorded [291]

A rare occurrence are the papulopustular generalized dense varioliform exanthems [93]

Tularemia

Tularemia is named after the California county of Tulare where it was first observed among squirrels by McCoy [294] In man it is usually acquired by the handling especially skinning of wild rabbits hares squirrels and other rodents or by eating the insufficiently cooked meat from them It has been shown to be carried by ticks [95 296] bedbugs [297] and other insects [98] Laboratory infections have occurred in a considerable number although no contagion from man to man has become known except for one case of a physician at an autopsy (Weil bacher and Moss after Robert[299])

The cause is a small pleomorphic gram negative bacterium *Pasteurella tularensis* which seems to be able to penetrate the unbroken skin as well as the mucosa The incubation period is most often four days but it varies considerably In traumatic infections the first symptoms at the site of the injury may develop after a few hours [300 301] Fever may break out suddenly before any other symptoms even before the primary lesion appears [30] This indicates the early dissemination of the infection If the infection begins in the skin which is by far the most common way a primary lesion develops and the disease spreads along the lymphatics The regional lymphatic vessels become indurated small nodules or bubonuli appear along them and bubos develop which may reach large size and may suppurate

If the infection occurs in the conjunctival sac (1 per cent Hurst after Tassman[303] 3 per cent after Pullen and Stuart[300] 12 per cent Vrla after Robert[299]) or in the tonsils characteristic clinical pictures of long lasting lid edema and suppurative lymphadenitis develop The typhoid resembling type without apparent portal of infection is very rare It has been seen in several laboratory infections The severity of the infection varies from mild ambulatory cases with little fever and no internal complications to illnesses of many months duration sometimes with a fatal outcome The mortality in the United States amounted

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[93] Teissier P Reilly J Cambe les and Cathala Form exanthématique de la pest bubonique Bull et mém S c méd d hôp de Par 49 8 4 831 192

[294] McCoy C W and Chapin C W Tularemia Bull 43 Hyg Lab U S P H S 1911

[295] Davis G E Philip C B and Park r R R I olation Fr m the Rocky Mountain Wood Tick of Bacterium Tula ense Am J Hyg 19 449-456 1934

[296] Byfield C N Breslow L Cro R R Jr and Hershey N J Tick Borne Tular mia J A M A 127 191 196 1945

[297] Bogenko V Bedbugs as Carri rs of Tular mia Vestnik mik 14 436 1935 Zbl 61 314

[298] Miller H E and Taussig L R Tularemia Arch D rmat & Syph 19 378 390 1929

[299] Robert F Tular mia R i w of Lit rature D rmatologica 80 98-107 1939

[300] Pullen R L and Stuart B M Tula mia ? 5 Cases J A M A 129 4 5 00 194

[301] Stuart B M Tularemia and Pn umonia Am J M Sc 201 9 3 194

[302] Bsteh O Die B ibon nform n d Tularämi Z ntralbl f Chir 67 1 48 1251 1940

[303] Tassman J S Eye M nif station of Internal Diseases St Louis 194 Th C V Mosby Company

to 4 8 per cent among 7 077 cases reported from 1924 to 1936 [304] The autopsy findings often resembled those of tuberculosis [30, 305] There are miliary gray foci in the enlarged spleen and less often in the liver and in the lungs which may show pneumonia or abscess The microscopic picture of the lymph nodes and the subcutaneous nodules is that of an infectious granuloma[306] with epithelioid cells lymphocytes and giant cells of the Langhans type creating a great similarity to tuberculosis [307]

The microorganism can be isolated from the blood of the patient by inoculation into guinea pigs and by culture This however is hardly possible after the first two weeks[308] and it has rarely been accomplished from an open lesion [309] Agglutination in serum dilutions above 1 80 is considered diagnostic [310] Skin allergy to tularemia[311] develops as early as four days after infection or even sooner [312] The intracutaneous test with 0 02 or 0 05 c c of a bacterial suspension is read after forty eight hours The disease seems to leave the patients immune

The treatment is symptomatic The value of antiserum derived from goats [313] which has been found effective in reducing the severity and duration of the disease [300] needs confirmation The beneficial effect of the sulfonamides is not generally confirmed [314] Streptomycin is now considered to be the drug of choice

Dermadromes —The primary lesion may occur almost anywhere on the skin It may be single or there may be multiple lesions The primary lesion appears after a period of about one week when general dissemination has already manifested itself by fever and malaise Even the regional lymph nodes may become enlarged and tender before the appearance of the primary lesion The initial lesion is a papule the center of which soon becomes depressed and necrotic forming a punched out ulcer with raised edges This ulcer is painful and defies therapy but after several weeks it heals spontaneously [308] The early lesions of tularemia may imitate syphilis anthrax felon or other conditions Due to the lymphatic chain of nodules or abscesses the picture may closely resemble sporotrichosis or primary inoculation tuberculosis [98, 315]

In the primary stage the diagnosis often can be secured only by the intracutaneous test

The bubonuli and lymph nodes may become tender adhere to the skin and ulcerate In one case reported by Blackford and Smith (quoted after Hitch

[304] Cumming H S Tularemia Bull Office Internat d hyg Pub 29 32 1937
[305] Gundry L P and Warner C G Fatal Tularemia 15 Autopsies Ann Int Med 7 837 85 1934
[306] Lawless J K Tularemia Arch Dermat & Syph 44 147 160 1941
[307] Cuy W H and Jacob F M Tularemia Arch Dermat & Syph 21 900 1931
[308] Hitch T M and Smith D C Cutaneous Manifestations of Tularemia Arch Dermat & Syph 38 859 876 1938
[309] Netherton E W Tularemia Cutaneous Manifestations Arch Dermat & Syph 16 170 181 1927
[310] Pasternack J G Tularemic Inguinal Buboes Following Tick Bite J A M A 112 1814 1817 1939
[311] Foshay L Tularemia Facilitated Diagnosis by Intradermal Reaction J Infect Dis 51 286 193
[312] Larson C W Interesting Case of Tularemia Tri State M J 13 2708-2714 1941
[313] Foshay L Tularemia Treated by a New Specific Antiserum Am J M Sc 187 23 245 1934
[314] Warling F H Tularemia 10 Cases J Oklahoma M A 35 103 106 194
[315] Shelmire B Tularemia Resembling Sporotrichosis Arch Dermat & Syph 19 918 0 1 1929

and Smith[308]) fungating growths developed out of such bubonuli The histological structure of the subcutaneous nodules is definitely tuberculoid

Generalized *eruptions* are a feature of the disease but they occur only in a fraction of the cases (8 per cent after Pullen and Stuart[309]) and are not characterized by any specific morphology Hitch and Smith[308] surveyed forty eight cases of secondary eruption in tularemia They demonstrated that eruptions occur in all types of the disease most often in the second week and that the average duration is three weeks However great deviation of the average figures is

Fig 35 —Tularemia Erythema exudativum multiforme resembling eruption on fifteenth day of the disease (From Hitch J M and Smith D J y C Arch Dermat 1938)



Fig 36 —Tularemia Papular rash (Courtesy Dr Walter M Simpson from Sutton and Sutton Diseases of the Skin The C V Mosby Company)

frequently observed Pleomorphism is a characteristic feature The most commonly encountered morphologic type was the *papular* eruption which was seen in approximately one half of the eruptive cases Less common are macules pustules vesicles wheals nodules ulcerations and transitional forms The rashes often gave the impression of erythema multiforme sometimes with herpes iris lesions The eruptions were generalized or they involved only a part of the body mostly the upper trunk and the arms especially on the side of the primary lesion In ophthalmic cases a facial eruption appeared on the side of the infected eye The eruptive cases did not differ from the noneruptive ones with regard to incubation period or agglutination titer The histological examination did not reveal changes other than one might expect that is edema and perivascular lymphocytic and fibroblastic infiltration The common appearance of the rashes after the period of bacteremia and fever supports the conception of the toxic rather than infectious nature of the secondary rashes in tularemia

The prognosis of the secondary rashes is good the treatment is symptomatic



Fig 37 —Primary lesion of tularemia and lymphangitis six weeks after onset (Courtesy Dr Walter M Simpson from Sutton and Sutton Diseases of the Skin The C V Mosby Company)

Erythema Arthriticum Epidemicum Ratbite Fever or Haverhill Fever

*Erythema arthriticum epidemicum ratbite fever Haverhill fever**—none of these three names is correct The disease is not always epidemic does not always follow a rat bite and Haverhill Mass is neither the only nor the first place where it was observed Erythema arthriticum would be a good name but the term Haverhill fever has become established

The disease is an acute infection which usually follows a rat bite It should not be confused with sodoku which is also transmitted by rat bites While the ratbite cases occur sporadically[318] a milk borne epidemic with eighty six cases

F Bibliography of the ratbite f e Brown T M and Nunemaker T G Bull Johns Hopkins Hosp 70 201 1942

318 Farr B F lo H C H and Nog I T Haverhill Fever Ca With Review of Literature Arch Int M 64 1 14 1939

was observed in Haverhill Mass in 1926[317, 318] and another milk borne—not quite verified—outbreak of 600 cases at Chester Pa (Armstrong and H Wood after Place and Sutton[318]) The epidemic and sporadic forms are caused by the nonmotile pleomorphic gram negative and nonacid fast *Streptobacillus moniliformis* (Haverhillia multiformis)[319] which during the fever can be cultured from the blood of the patient Mice die from the disease forty eight hours after intra peritoneal injection of blood

About three days after the infecting bite of rats who often harbor the microorganism in their pharynx the disease starts quite suddenly with malaise headache chill and high fever A rash and acute polyarthritis develop early and heal after several days There is a leukocytosis of over 12 000 The spleen is not enlarged There were no fatalities in the Haverhill epidemic A *rash* was observed in 94 per cent of the Haverhill cases which appeared during the first week most often between the second and fifth days It involved predominantly the lateral and distal extensor surfaces of the extremities rarely the trunk and face There is sometimes accentuation around the joints[318] The exanthem has been described as a maculopapular rubelliform or morbilliform vividly red eruption with the efflorescences being about 3 to 5 mm in size[320] In some cases the exanthem had the characteristics of erythema exudativum multiforme (Levaditi Nicolau and Poincloux after Farrel and associates[316]) The rash usually fades after one week with little desquamation or pigmentation The exanthem may reappear with new paroxysms of the fever Then it is likely to be more confluent[320] A *hemorrhagic tendency* can be demonstrated by a positive tourniquet test and by pin point hemorrhages in the center of the lesions

In the cases studied by Allbritten Sheely and Teffers[320] tender purpuric nodules with yellow nonsuppurative depressed centers resembling those seen in subacute bacterial endocarditis appeared around the finger tips They probably are metastatic embolic foci Lymphadenopathy in relation to the site of the bite is rare[320]

The *diagnosis* rests on the history of a rat bite and the laboratory findings Agglutination tests are known A cutaneous reaction to suspensions of killed streptobacilli was present in 83 per cent of the Haverhill patients tested late in convalescence It seems important to compare the symptomatology of Haverhill fever and that of sodoku the other ratbite disease which may occasionally cause a syndrome quite indistinguishable from Haverhill fever[321] Usually sodoku (see under sodoku) presents a chancriform induration at the bitten area which is followed by lymphangitis Arthritis is rare The causative organisms of both diseases are penicillin sensitive (Wheeler after Pleming[8a])

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[317] Place E H Sutton L E and Willner O Erythema Arthriticum Epidemicum Preliminary Report Boston M & S J 194 285 87 1926

[318] Place E H and Sutton L E Haverhill Fever Arch Int Med 54 659 1934

Larkey F Jr and Hudson N P Haverhill Fever Am J Path 2 357 1926

[320] Allbritten F F Sheely R F and Jeffers W A Haverhill Multiformis Septicemia Relationship to Haverhill and Ratbite Fevers J A M A 114 2360 2363 1940

[321] Brown T M and Nunemaker J C Ratbite Fever Review of American Cases Bull Johns Hopkins Hosp 70 201 1942

Glanders (Malleus)

Glanders (malleus) occurs predominantly and in large epizootics among horses from which most of the rare human cases originate A number of laboratory infections have become known [32] The disease which has an incubation period of from three to five days is caused by the pleomorphic nonmotile bacillus *Malleomyces mallei* The germ enters the human body through the skin or through the mucosa possibly without a wound From a primary lesion the disease spreads and frequently becomes generalized taking an acute or irregularly relapsing chronic course of unfavorable prognosis Specific lesions may occur in any organ but there is a definite cutaneous and mucosal affinity The predominantly lymphangitic form is sometimes called farcy while the term glanders is often used for those cases in which the mucosal especially the rhinitic involvement dominates the picture Not very long ago the two forms were believed to be different entities The specific malleus lesions are granulomas which resemble tuberculosis in many ways

The *diagnosis* rests on a history of contact with horses or mules the unusual clinical picture the microscopic and cultural evidence of *Malleomyces mallei* the intraperitoneal inoculation into the male guinea pig followed by the specific inflammation of the testes and various serological and allergic tests among which the complement fixation the ophthalmic and the intracutaneous tests have been used in man

Dermadromes —The primary lesion which has been most often observed on the hands and arms the face and the conjunctiva is a furuncle like infiltration which soon breaks down in the center and forms an ulcer with jagged raised livid and infiltrated edges and a necrotic floor with edematous and erythematous surroundings [33] The lesion may reach dollar size but it finally heals spontaneously In some cases it fails to develop so that lymphangitis appears as the first cutaneous symptom Lymphangitis without noticeable lymphadenitis is a peculiar feature of malleus in human beings [33] The wire or pencil like lymphatics are palpable along the extremity and small bubonuli (buds) develop alongside the vessels This type of lymphangitis resembles sporotrichosis or tuberculosis Sinuses sievelike perforations ulcers and scars may develop In rare instances the disease becomes chronic in this stage The primary lesion of the oral or nasal mucosa is an ulcer similar to that of the skin

General *systemic* infection follows the majority of the primary lesions The period after which systemic symptoms appear may be a few days to many weeks or months The skin manifestations of the systemic infection have a predilection for the nose and face These secondary malleids appear in crops and show great differences in severity grouping and number The exanthem usually starts as a roseola The maculae which in rare instances are purpuric become papular papulopustular and later ulcerative They are occasionally bullous or composed

[32] Ro l ffs J W Acut Glanders Ca [illegible] d rl tijd br g ne sk 2 3 72 3781 19 9 Zbl 32 29

[33] Bi rbaum K and Gottron H Rotz (Malleus) Hanlb d H u Ck 9 355-306 1 9

of concentric rings[3,4] resembling erythema multiforme These ulcers may by infiltration of the surroundings and by coalescence grow to larger plaques which may also develop from cutaneous or subcutaneous nodules Breaking down of nodules or plaques may cause deep destruction of the muscles and tendons and even affect the joints[3,3] Destructive and suppurative lesions in and around the nose may cause a peculiar swelling and erythema of the nose which has been termed by de Balogh[5] who reported eight cases potato nose This author describes nonsuppurative livid nodules in the face as typical secondary lesions

The *histology* of the fully developed lesions shows granulation tissue composed predominantly of leukocytes and to a lesser degree of epithelioid plasma and mast cells There is a pronounced necrotic tendency Karyorrhexis is a feature and bacilli may occur in large numbers

Sporotrichosis tuberculosis and pyogenic lymphangitis must be considered in the lymphangitic period and syphilis and mycosis fungoides in the later systemic stages The common concentration around the nose and the necrotic tendency of the granuloma support the clinical diagnosis of malleus However considering the rarity of human glanders and the many varieties of its course all laboratory methods must be employed

Generalized glanders in man is almost without exception a fatal disease Chronic localized malleus heals spontaneously in about 50 per cent of the cases (Bollinger after Bierbaum and Gottron[3,3]) No specific treatment is known

Cholera Asiatica

Cholera asiatica is an acute often epidemic infection caused by the *Vibrio comma* (Koch) In its severest fulminating form the disease may run a fatal course in from three to four hours but less severe forms are well known The outstanding symptoms are excessive watery diarrhea dehydration and circulatory collapse

Dermadromes —The skin is described as pale or cyanotic even livid covered with sweat wrinkled and withered Urea frost has often been seen covering such dehydrated patients In fact this sign was described in cholera long before its association with uremia was noted (Schottin after Chargin and Keil[3,6]) In cholera there is a pronounced tendency to necroses and decubiti[3,7] Exanthems are infrequent

The older literature contains a number of references Liebermeister[3,8] in a monograph written after the great epidemic of 17 000 cases in Hamburg Germany in 1892 denied the existence of a specific exanthem at the height of the disease In the early stages of recovery cyanotic spots may remain as remnants

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[4] Lösing A Über einen Fall von akutem Rotz B uns B itr klin Chi **125** 433-443 19

[5] Balogh F d Skin Lesions in Human Glanders V rh 9 Internat Kongr Dermat **2** 427-431 1936

[6] Chargin L a 1 I II H Skin Disease in Nonsurgical Renal Disease Arch Dermat & Syph **26** 314-335 193

[37] Elias H and Doe R Cholera Asiatica Handbuch der inneren Medizin Berlin 19 5 Julius Springer

[38] Liebermeister C Cholera Asiatica and Cholera nostras Nothnagel s Specielle Pathologie und Therapie VI a 1896 Alfred Hölder

of the collapse of circulation during the attack Roseola and other erythemas especially of the erythema multiforme type papules vesicles urticaria and petechiae have occasionally been seen but the specific character of these rashes has not been demonstrated Some may have been drug eruptions [3 7]

Whooping Cough

During the characteristic attacks the glottis is temporarily closed and at the termination of the spell it is opened for a long drawn crowing inspiration [329] The disease is caused by a small bacillus with accentuated poles discovered by Bordet and Gengou

Dermadromes —The repeated severe coughing spells frequently produce some puffiness around the eyes especially of the upper lids together with slight chemosis This is known as the *whooping cough face* *Petechiae* which are quite rare in the skin occur more frequently in the mucosae especially in the conjunctivae of young children Both bulbar *conjunctivae may be deep red* a terrifying but harmless sign

The vesicles of a *varicella exanthem* coinciding with whooping cough may *become hemorrhagic* due to the coughing bouts This is especially true of the vesicles in the area drained by the upper vena cava [329] The violent fluctuations of vascular pressure during the cough and possibly the infectious and toxic damage to the capillaries may prepare the rhexis of the capillaries

Cutaneous *emphysema* is a rare but dangerous complication of whooping cough It is caused by the rupture of alveolar vesicles due to the high intra pulmonary pressure From the ruptured lung the air is pressed under the pleura which on autopsy has been seen to be separated from the lung The air follows the mediastinum and finally reaches the skin of the neck or chest

A well known complication of whooping cough is the shallow *ulceration of the frenulum linguae* It results from injury and irritation of the frenulum caused during the coughing by the incisor teeth or in the absence of teeth by the hard lower jaw

Diphtheria

Exanthems indicative of generalized diphtheric infection are rare Some rashes have been interpreted as initial exanthems since they occurred during the first day [330]

Purpuric morbilliform scarlatiniform papular and vesicular *eruptions* resembling erythema nodosum and multiforme and even typhoidlike rose spots have been described Allowance must be made for drug eruptions true scarlet fever [331] and serum exanthems

Herpes seems to be rarer than in many other infectious diseases The herpes vesicles may contain bacilli (Rall after Biberstein[330])

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1 Knoepf lmacher W Whooping C ugh Pfaundler an l S hlossmann The Dis ase of Children vol III Philad lphia 1935 J B Lippincott Company pp 3 6 351

330 Bib rst in H Di Diphth ri der Haut Han lb d H u C k 9 1 145 19 19 0

Bru a P Esant mi scarlattiniformi e I rot rapia n l corso d lla dift it Scritti m i dedicati a Carlo Comba Riv di clin p diat 27 4 6-438 19 9

Panniculitis (Weber-Christian Disease)

Twenty eight cases of a syndrome of relapsing febrile nodular nonsuppurative panniculitis (Weber Christian disease) have been reported since 1892 [83] There are crops of cutaneous and subcutaneous painless or tender nodules mostly on the thighs and arms but also on the trunk and accompanied by fever The lesions are the expression of an inflammatory process which results in atrophy of the subcutaneous fat producing in the skin lasting depressions of a varying depth and width Fever is a constant symptom Two cases were fatal The etiology and even the clinical entity itself are still controversial Focal infection tuberculosis eruptions from iodine or bromides and other causes have been considered[333])

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[83] Pfeifer V Ueber einen Fall von herdw s r Atroph des subcutanen Fettgewebes Deut ches Arch f klin M d 50 438 449 189?

[333] La kin V P De Sanctis A C and Ma gulis A E Panniculitis—Review of Literature Am J Dis Child 67 1 0 1? 1944

Chapter IV

SYSTEMIC INFECTIONS

Influenza

Influenza is almost certainly caused by at least three different types of virus [334] now called A B and V but is usually complicated by the secondary invasion of various bacilli especially the Pfeiffer bacillus the pneumococcus and the pyogenic cocci Sporadic cases occur although epidemics and pandemics are characteristic of the disease Influenza is very contagious The incubation period is short about two days The onset is quite sudden sometimes *with marked catarrhal symptoms or sore throat* The fever is irregular and chills and remissions are common The respiratory tract in its full length is inflamed bronchitis and pneumonia are serious complications which in 1918 caused most of the deaths [85] Prostration is often marked and not explained by the temperature *alone Gastrointestinal symptoms and sometimes severe and irreversible* lesions of the nervous system may in a small minority of cases dominate the picture Many other complications are known Mild leukopenia is common *before secondary infection supervenes*

The post mortem findings concern chiefly the respiratory tract

The mortality varies from 15 to 60 per cent depending on the character of the epidemic[335] although exact figures are not available In 1918 1919 at the time of the last influenza pandemic there were 550 000 deaths in the United States in excess of the normal expectancy No specific treatment has been discovered as yet

Dermadromes —The skin manifestations are neither impressive nor of diagnostic importance They rarely influence the course or cause suffering to *the patient* [336] *The incidence of skin and oral symptoms given by various authors* varies from 1 to 20 per cent However such percentages are of little value in a disease which in many cases is difficult to differentiate from other common respiratory infections

During the febrile period *herpes* simplex is common and sometimes develops even after the temperature has returned to normal The appearance of herpes does not seem to depend on the respiratory involvement [337]

Exanthems of great variability have often been noticed usually in the early stages of the infection These skin eruptions are most often macular[338] or mor

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[334] Horsfall F L Jr Present Status of Influenza J A M A 120 284 87 1941

[335] Top F H Communicable Diseases St Louis 1941 The C V Mosby Company

[85] Schütz H Dermatologie und Grippe Med Welt 13 1506 1510 1939

[337] Schumacher C and Moncorps C Haut- und Schleimhauterkrankungen bei Grippe 711 16 89 94 102

[338] Freund Grippeexanthem 7bl 23 6

bilWith form[339] less frequently scarlatiniform[340] Besides these main types urticarial vivid red papular[341] purpuric and spotted typhuslike rashes have been recorded There are combinations of macular and hemorrhagic lesions[34] The serious prognostic significance of purpuric rashes is often emphasized Erythema nodosum and erythema exudativum multiforme[343] have been observed in a considerable number of cases

Most of the influenza rashes are very transitory[339 344] The difficulty in differentiation from measles scarlet fever and other exanthematic diseases is often great A carefully taken history of contacts and previous diseases consideration of the incubation period and negative results of the diagnostic procedures used in other infections will usually help to overcome the difficulties In sporadic cases the diagnosis may be made only after further observation of the course Jordan[344] emphasizes the lack of adenopathy as a criterion against rubella



Fig 38 —Vi u tongue in influ n a Th tongu I large flabby and shows dental impressions (C urtesy Dr Max Fox)

In the *oral* mucosa circumscribed erythema of the soft palate and the posterior tongue and a buccal exanthem not unlike Koplik s spots in measles are common[337] A flabby slightly edematous tongue showing marginal impressions of the teeth (virus tongue) is often considered characteristic of influenza and other virus di eases The pharyngeal involvement may occasionally become severe Follicular tonsillitis pseudomembranes of the pharynx and small ulcerations of the mucosa may even lead to glottic edema

[339] Opit H Grippe xanthem I in I rärztl Praxis 6 154 1 6 1935

[340] I och H E anth m b i grippe n F krankungen Wi n med Wchnschr 78 85 19 8

[341] Dessy C Sulle manif ta ioni papulari cutan e nella influen a Riforma med 53 815-819 1937

[343] Leicht nt itt B and Schob r W Gripp exantl me I lin Wchnschr 3 10 9 103 19 4

[344] Oppenheim Gripp exanth m Zbl 38 743

[344] Jordan A U ber Grippeausschläg Dermat Wchnschr 91 1011 1014 1930

Following the acute period erysipelas of the face has often been observed especially in the older epidemics Other common cutaneous sequelae are furunculosis and herpes zoster Symmetric gangrene of the extremities is an exceedingly rare event[345]

Alopecia diffusa was a common dermadrome during the epidemic of 1918 The shedding of the hair after influenza was often troublesome although the hair usually grew back Beau s lines of the nails were often observed The dermadromes of influenzal encephalitis will be discussed in Chapter XXXIX

Measles

It is generally agreed that measles is caused by a filtrable virus which lately has been cultured in the chick embryo[347] (Kunert and Wenkebach after Rietschel[346] and successfully inoculated into the child after several passages



Fig 39 —Measles fifth day Exanthem and conjunctivitis (Courtesy Dr Ma Fox)

The disease is highly contagious among persons who have not had much exposure to the virus and therefore is predominantly a child s disease Measles

[345]Mott A Gangrène aiguë symmétrique des extrémités post grippale Gaz méd de France 46 649 650 1939

[346]Rietschel H Measles Review of Literatur Monatschr f Kinderh 88 31 35 1941

[347]Rake G and Schaffer M F Studies of Measles Use of Chorio-Allantois of Developing Chicken Embryo J Immunol 38 177 1940

is most contagious about twenty four hours before the eruption With the appearance of the exanthem the infectivity decreases rapidly and is nil at the time of desquamation The infectious agent is present in the respiratory tract and in the blood and it has also been demonstrated in artificial blisters of the skin Lifelong specific immunity after measles is the rule true reinfection being extremely rare

The first catarrhal symptoms appear not too suddenly after an incubation period of about ten days Headache anorexia conjunctivitis and coryza sometimes with nosebleed cough vomiting and sudden fever are the common prodromal symptoms On the first day the lower lids may be slightly puffy and a fairly definite erythematous transverse line appears across the conjunctival surface of the lower eyelid about a third of the distance from the lid margin to the fornix (Stimson after Sobel in Mackee and Cipollaro[144])

On the second day of the prodromal stage a few (from six to twenty) pin point sized white spots often surrounded by a bright red at first narrow but soon widening areola appear on the buccal and later often on the labial mucosa This prodromal mucosal eruption which is commonly known as Koplik s spots is of great diagnostic importance since it hardly occurs in other diseases and it can be seen in about 90 per cent of the measles cases preceding the outbreak of the exanthem The Koplik spots vanish when the rash appears and are soon followed by an enanthem of dark red spots of pin head to lentil size which may coalesce into large spots scattered over the soft palate and later over greater areas Koplik s spots may be absent in the measles of small children [348]

The temperature usually drops on the second day only to rise again during the next two days Between the third and fifth days (two weeks after the infection) the rash appears The disease reaches its height around the fifth day and from that time on the symptoms are eased On the seventh or eighth day after the full development of the rash the temperature gradually becomes normal the rash fades and the catarrhal symptoms are no longer annoying Recovery follows gradually Cervical adenopathy is common but is mild and rarely leads to abscesses

The clinical picture is dominated by the rash and the intense catarrhal involvement of the mucous membranes particularly of the respiratory tract and of the eyes There is leukopenia at the height of the rash mainly caused by a drop in the lymphocytes

The list of possible complications is long but fortunately the overwhelming majority of the patients recover uneventfully

Dermadromes —Pale scarlatiniform or macular *premonitory rashes* are rare and very fleeting[349 350 351] and may disappear before the outbreak of the measles rash

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[348] Glanzmann E Das kritische Dreitagefieber exanthem mit rkl in n Kinder (Exanthema ubitum) F g bn d Inn Med u Kinderh 29 65-89 19 6

[349] Soucek A Masernbeobachtungen prodomales Exanthem M d Klin 23 1889 19 7

[350] Wieland E Ueber flüchtige scarlatiniform n Rash bei Masern Monatsch f Kinderh 42 48 -495 19 9

[351] Nöthen F J Vorexanthem bei Masern Jahrb f Kinderh 95 211 19

The *exanthem*[353] (Von Pirquet in Von Groer[35]) starts with pale pink spots from 1 to 5 mm in diameter. Intense itching may accompany the eruption. The spots are seen clearly first on the scalp behind the ears and between the shoulder blades, less distinctly around the mouth and nose and in front of the ears. The cheeks offer a certain resistance but are soon invaded also. On the second day a dense exanthem appears on the back and although less pronounced *on the chest, abdomen and mesial aspects of the arms. On the third and fourth* days the development is completed with the invasion of the legs. The emphasis

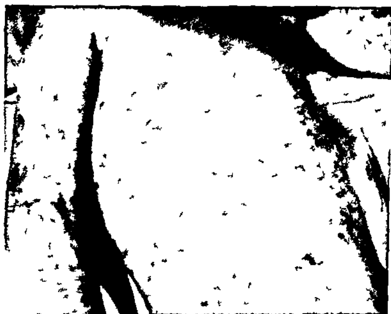


Fig 40 — Measles (Courtesy Dr Ma Fo)

is on the head, trunk, shoulders and anterior surfaces of the arms and thighs. *On the fifth day the appearance of new lesions usually stops.* With the return to normal temperature the spots fade in the order of their appearance leaving a pigmentation which is sometimes quite pronounced on the forehead. There is a superficial branny desquamation which usually starts on the face from two to five days after the appearance of the exanthem.[354]

The first lesions are follicular spots or slightly palpable papules surrounded by an anemic halo. They grow quickly in size and number and become confluent but the original follicular papular character can still be recognized within the larger bright red spots of the developed exanthem. There is a great variability

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[353] Von Groer, F: Measles, Pfaundler and Schlossmann: Diseases of Children, v 1, III, Philadelphia, 1935, J B Lippincott Company, pp 170-21

[354] Rolly, F: Akute Exanthem, Handbuch der inneren Medizin, vol 1, Berlin, 1925, Julius Springer

[35] Reuland, A: Ueber Hautschuppung nach Masern, Jahrb f Kinderh 115: 20 24, 1927

in the exanthems with regard to size of lesions density and tendency to remain discrete or become more confluent At its height the eruption is blotchy and dusky red Miliary vesicles are quite common on the follicular papules Increased seborrheic activity makes the skin feel greasy The tourniquet test is usually positive

While the exanthems may vary great similarities of the rash in siblings as well as in individual epidemics have been observed indicating the power of constitutional and microbic factors

The histopathology of the measles[355] exanthem is characterized by vacuolization in the epidermis and a perivascular predominantly lymphocytic infiltrate in the papillary body There are small necrotic areas which correspond to macroscopic pustules The absence of a horny layer in the oral mucosa produces the early erosions of the Koplik spots It is not for very long that anything has been known about the peculiar formation of giant cells with 50 to 100 nuclei which occur in the lymphatic tissue of the tonsils the respiratory tract and the esophagus and which have been seen in appendices removed during measles (Warthin and Finkelday after Ravina and Levy Lang[355] Manigi and Minami after Rietschel[346])

Among the *anomalies* of the exanthem must be named first its absence morbilli sine exanthemate Usually the Koplik spots too are absent in such cases[353] of which a great number have been well corroborated by the presence of all other symptoms by the incubation period and by contact cases[356 357]

While miliaria is common bullous measles are rare Confluent large bullae may though rarely cover and denude large areas so that the clinical picture of pemphigus results[358] Hemorrhagic measles is rare this variety has been seen in combination with bullous measles[359] Swelling of the upper lip of two to three days duration is in some epidemics so common that one author has spoken of a measles lip (Oxenius after Robert[360])

Measles especially the hemorrhagic form is sometimes followed by gangrene of localized areas of the skin[361 36] Related to these cases are the multiple ulcerations which are known as *ecthyma gangrenosum*[363] which are occasionally seen after other infections too usually affecting infants Ecthyma gangrenosum starts on the buttocks with hemorrhagic necrotic nodules or larger foci of cellulitis and leads to deep punched out ulcers The mortality is high The condition is probably caused by secondary infection especially with pyogenic cocci and *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*)

[355] Ravina A and Lévy Lang P Histologic Diagnosis of Measles Specificity of Giant Cells Appendicitis Caused by Measles P méd 45 8 1 82 1937

[356] Grassmann E Masern ohne Exanthem bei der Geschwistern Monatschr f Kinderh 27 510-511 1914

[357] Koppe H Masern ohne Exanthem Arch f Kinderh 84 190-193 1928

[358] Sthig r C Pemphigoid (bullöse) Masern and Pemphigus bei Masern Monatsch f Kinderh 27 3 5 335 19 4

[359] Linehan J J Hemorrhagic Measles Brit M J 2 7 5 1942

[360] Robert P Infectious Skin Diseases Other Than Tuberculosis and Leprosy Review of Literature Dermatologica 87 310-332 1943

[361] Thorp E A Case of Gangrene Following Measles Lancet 201 754 1921

[362] Wi stead J A Gangrene of the Foot Following Measles J Pediat 6 38 384 193

[363] Takahashi Ekthyma gangränosum im Verlauf von Masern Arch f Dermat u Syph 120 739-780 1914

Measles may affect *pre existing skin diseases* in various ways Infantile eczema[364] and prurigo[363] are often aggravated during measles[365] either by internal causes or by scratching during the itching eruption and desquamation periods Psoriasis seems to improve but returns during convalescence[364] Measles like other acute infectious diseases often weakens the cutaneous tuberculin reaction The predisposing influence to skin tuberculosis is recognized[366] Disseminated exanthematic apparently hematogenous cases of lupus vulgaris and tuberculosis cutis verrucosa are not very rare after measles in countries where skin tuberculosis is more prevalent than in the United States

German Measles (Rubella)

The term German measles resulted from the long combined efforts of German clinicians of the nineteenth century to separate a mild measles like contagious disease from typical measles When the International Medical Congress in London in 1881 tried to clarify the situation it was natural to speak of English measles and of German measles Since then the entity has become widely recognized but there are still some dissenting unitarians To prevent confusion it should be emphasized that the latin term rubeola is used for this disease in the German literature while in the English American terminology rubeola designates true measles (Dorland) The term rubella seems to be used only in the English speaking countries

The cause of the disease is unknown Children of 3 to 10 years of age are usually affected but no age group is immune Lasting immunity after the disease is the rule

The disease is best characterized by the often used expression mild measles The prodromal symptoms of malaise fever coryza and sore throat which are not always present are much less pronounced than in measles Children with German measles frequently come to the office of the dermatologist or are sent *home from school because of the rash* while a child with true measles is usually too sick to be ambulatory

The incubation period of rubella is from two to three weeks The fever is moderate and there is no photophobia or conjunctivitis Excessive perspiration during the first to second prodromal days is a peculiar symptom (Stolte after Rietschel[367]) The palate and uvula are reddened and a few red follicles often appear along the midline (Forchheimer's sign) but there are no Koplik spots *and the catarrhal symptoms if any are mild*

General *lymphadenopathy* is such an outstanding feature of the disease that Glanzmann advanced the theory that rubella is a disease of the lymphatic system not primarily an exanthem and therefore *toto caelo* different from measles

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[364] Beek C H Immunity Against Psoriasis in Patients Who Have Previously Had Measles Nederl tijdschr v Geneesk 79 4157-41 9 1935

[365] Costantino C Sul comportamento dell eczema del lattante durante il morbillo Clin pediat 12 216-228 1930

[366] Volk R Tuberkulose der Haut Handb d H u Gk 10 1 1931

[367] Rietschel H Rubella Monatschr f Kinderh 88 342 35 1941

and scarlet fever Almost all the peripheral lymphatic nodes are swollen and tender and the mastoid occipital and posterior cervical glands particularly of the left side are so enlarged that the swelling often is not only palpable but visible The lymphadenopathy starts before the exanthem and may outlast it by several weeks This generalized lymphadenitis may be the only sign of rubella In such exanthemless cases the diagnosis must depend on the accompanying circumstances for example contact cases with exanthem [370]



Fig 41 —German m a les Quit coplou ra h (Courtesy Dr Max Fo)

The blood shows an initial leukopenia and a later eosinophilia (8 per cent) In the course of the disease the leukocytes rise and the increase of the plasma cells becomes marked reaching 12 per cent [371 3]

The *prognosis* is very favorable The *treatment* is symptomatic

Dermadromes —The exanthem which appears on the second or third day follows in many ways the pattern of measles It is usually seen first behind the ears and on the no e but within one day it involves the whole body occasionally large areas remain free The fresh spots are rounder more clearly defined and more regular than those of true measles The most common size is that of a split pea although the rash may consist of smaller or larger spots The color is

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[8] Ri tsch l H Acut Infectiou Exanth m Th Di ases of Childr n By Pfaundl Schlossmann P t rman vol III Philad lphia, 1935 J B Lippin ott Company pp 213 233

[9] Rietsch l H Mas rn und Röt ln Monatschr f Ki d rh 71 54 60 1937

[1] Höjstrup G Rubella With ut a Rash Brit J Child Di 20 20 3 19 3

[1] Mo aw tz C Röt ln Rubeola Handb d H u 14 1 4 7-429 1930

[73] F u shack Röt ln Th rap d C g nw 68 76-77 192?

red a shade less bright than in true measles and fades quickly Often a confluent erythema develops on the face The skin between the spots may especially on the back be diffusely red with the progress of the disease Some epidemics have a pronounced hemorrhagic component [368] The rash appears in successive crops each of which lasts about twenty four hours The whole exanthem lasts about three days It fades in the order of the eruption [369] occasionally with a light dusty desquamation and faint pigmentation [353] The face and neck may be cleared while the legs are still red



Fig 4 —German measles Postauricular lymphatic nodes (Courtesy D Max Fox)

The pharynx is diffusely red and the tongue often resembles the raspberry tongue of scarlet fever that is it is diffusely red not coated and the fungiform papillae are swollen

Roseola Infantum (Exanthema Subitum)

John Zahorsky [373,374] of St Louis (in 1910 to 1913) separated from various little understood exanthematic diseases of childhood a typical entity to which he unfortunately gave the old name of roseola infantum The term erythema

373 Zahorsky J Roseola Infantum Survey of Literature Arch Pediat 57 405–409 1940
374 Zahorsky J Roseola Infantum In J Brennemann s Practice of Pediatrics vol II Hagerstown Md 1937 W F Prior Company Inc

subitum[375] has become more popular while Glanzmann's[348] unwieldy name critical three days fever exanthem of the infant is used only rarely

The disease is an acute infection which at least in some countries attacks a large percentage of the infants Rosenbusch[376] estimates that about 50 per cent of the young children become infected mostly at the end of the first year of life rarely after the third year

The etiology is unknown but influenza has been suspected[377] The incubation period is seven days (from five to fifteen days Sobel[144]) Lasting immunity results from the infection but a few cases of repeated attacks have been observed[374, 378] About 40 per cent of the cases occur in summer and only 18 per cent in winter[379]

The clinical picture is characterized by three days of continuous high fever and the eruption of a morbilliform rash immediately after the critical end of the fever The onset is sudden sometimes alarming with convulsions[380] headache and vomiting Sometimes however the children do not complain in spite of the fever Complications are almost unknown and in many cases the general well being is not disturbed Coryza and other mucosal symptoms and adenopathy are mild There is a characteristic drop of the polymorphonuclear leukocytes (2 to 20 per cent) and a relative lymphocytosis and mononucleosis (80 to 98 per cent)[348] These findings are most marked on the third day[375] The spleen is not enlarged The prognosis is invariably favorable in spite of the sometimes alarming onset

Dermadromes —The *rash* appears as Glanzmann[348] poetically puts it as the aurora of recovery after the fever period It starts on the back and covers the trunk within twelve hours sometimes leaving the face the scalp and the extremities free A second crop may then cover the limbs and remain visible when the first eruption has faded The rash consists of slightly raised rose spots from 2 to 5 mm in size confluent or in irregular groups between which are small areas of normal skin Later a large confluent erythema may appear on the back suggesting scarlet fever There is no pruritus and the rash disappears in two or three days without pigmentation or desquamation There is no characteristic enanthem an important differential feature

The diagnosis may be difficult especially in isolated cases The most important feature is the eruption at or after the fall of the temperature on the fourth day In measles the rash appears at the height of the disease the whole syndrome is more severe and infections among siblings are common In scarlet fever there is sore throat a typical tongue the exanthem appears early and

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[375] Veeder B S and Hempelmann T C Exanthema Subitum J A M A 77 178 1789 19[illegible]
[376] Rosenbusch H Exanthema subitum Schweiz med Wchnschr 69 1173 1175 1939
[377] Opitz H Masern Exanthema subitum Lind ärztl Prax 10 6 8 1939
[378] Barenberg L H and Greenspan L Exanthema Subitum Am J Dis Child 58 983 993 1939
[379] B[illegible] B B J Roseola Infantum in New York State J Med 41 1854 1859 1941
[380] Cronthal R N Roseola infantum Wiscon in M J 40 -5 7 1941

lasts much longer and there is desquamation and leukocytosis Rubella which may look very much like roseola infantum has the characteristic lymphadenopathy Erythema infectiosum rarely causes fever and the exanthem starts on the face especially over the bridge of the nose Drug eruptions and toxic and infectious erythemas must be considered No specific therapy is known

Erythema Infectiosum

Erythema infectiosum which is also known under a number of other names for example fifth disease and megalerythema, is a moderately contagious infection of unknown cause usually affecting children The disease occurs in epidemics of relatively small size often in institutions The outbreaks are usually in late winter and spring Animal inoculation and bacteriological studies have not been successful However children have been infected by injection of blood taken at the height of the rash and by pharyngeal mucus [381]

The incubation period is about nine to fourteen days but it was only twenty four hours in the experimental infections There are no or very slight prodromes The disease starts suddenly with a *rash* which is the main and sometimes the only symptom The exanthem appears first on the face as small red spots which soon grow and coalesce forming an erythema which is most pronounced over the cheeks and which leaves the perioral and periocular areas pale The erythemas of the cheeks are often connected by a red isthmus over the base of the nose so that a butterfly figure results The erythema is usually bright red[38] sometimes pink or cyanotic [383] the fairly well defined edges are slightly palpable and raised and the surface is smooth and in severe cases hot to the touch The chin is seldom affected the forehead is more often affected The patient looks as if he has been slapped on both cheeks so definite is the erythema [383]

One to two days later the erythema usually appears on the outer surfaces of the upper arms and sometimes on the buttocks and extensor aspects of the thighs[383 384] The lesions are slightly papular and have a tendency to grow peripherally and to fade in the center Thus ring shaped garlandlike zigzag lattice [385] honeycomb and other patterns result The hands and feet are not affected There is only slight fever no enanthem and little itching From the third to the twelfth day the eruption fades but relapses may occur up to several months later Atypical rashes affecting only the limbs are rare [386 387] Desquamation is usually lacking In a small portion of the cases the face remains free [386] There

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[381] Taccone C Sulla quinta malattia Nuova epidemia osservata a Milano Pediatria Arch di pat e clin pediat 3 77 126 19 8 Zbl 31 920

[382] Chargin L Sobel N and Goldstein H Erythema Infectiosum Arch Dermat & Syph 47 467-477 1943

[383] Tobler L Erythema Infectiosum Ergebn d inn Med u Kinderh 14 70 98 1915

[384] Romeo Lozano A Erythema infectiosum Pediatria espan 23 307 3 0 1934 Zbl 61 55

[385] Kissinger P Erythema infectiosum München med Wchnschr 19 8 II 1381

[386] Lawton A L and Smith R E Erythema Infectiosum Epidemic Arch Int Med 47 28-41 1931

[387] Rector J M Erythema Infectiosum—Clinical Observations J Pediat 15 540-545 1939

is moderate lymphocytosis and eosinophilia of 6 to 11 per cent[369, 388] (Zikowsky[389] 20 per cent) during convalescence and later mononucleosis Lymphadenopathy is uncertain The children twice as many girls as boys[387] are but little disturbed Complications are hardly ever seen and fatalities have not occurred

Febris Herpetica, Febris Ephemera, Febricula

Febris herpetica febris ephemera and febricula comprise a group of fevers of unknown etiology characterized by a high temperature for about one day *with the usual complaints of an acute febrile disease In many of these short* fevers *herpes labialis* appears, usually with sinking temperature or one or several days after the bout[390]

Rubeola Scarlatinosa, or Fourth Disease, Dukes-Filatow Disease

Rubeola scarlatinosa is also called fourth disease and Dukes Filatow disease There is much objection[368] to the acknowledgment as an entity of a febrile exanthem of which a few small epidemics have been observed

After an incubation period of from nine to twenty days that is much longer than in scarlet fever the disease starts with a pink scarlatiniform slightly papular exanthem which covers the body within a few hours and does not always leave the circumoral area free The face is generally less involved than the other parts The rash fades after one to three days and is followed by a slight branny desquamation The pharynx is red and the tongue only slightly coated

The fever is mild and does not last longer than the rash There are no important complications[353] There is no cross immunity with scarlet fever the mild cases of which the disease resembles

Miliary Fever (Sweating Sickness)

About 200 epidemics of miliary fever or sweating sickness have been described since the first outbreak frightened London in 1486[391] No sporadic or endemic cases have been observed The epidemics usually occurred in spring or summer in an explosive form commonly restricted to relatively small areas like cities or valleys The mortality of the epidemics varied from 0 to 90 per cent with an average of 8 per cent in the nineteenth century This is a greater fluctuation than is known of any other epidemic disease The horror caused by the high mortality of some of these epidemics was augmented by the sudden outbreak and the fulminating course Frequently persons who had been in good health died within one or two days More recently epidemics have occurred

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[388] Naegeli O Blutkrankheiten und Blutdiagnostik ed 5 Berlin 1931 Julius Springer

[389] Zikowsky J Erythema Infectiosum Wien klin Wchnschr 1933 II 843 847

[390] Hirsch C Febris herpetica Wien a 190 Alfred Hölder

[391] Hirsch A Der Friesel vom historisch und geographisch pathologischen Standpunkt Virchows Arch f path Anat 8 454 523 1855 9 166 171 1856

in France[39] and Southern Germany and perhaps in Rumania[391] The last certain outbreak was observed in some French hamlets by L Rousseau[392] in 1926 with hardly any variations from the classic picture No epidemics have become known in America[85] The cause of the infection is unknown The incubation period[353 394] seldom exceeds one to two days but was found to be from ten to fifteen days in the cases of Stroé and Stroé[393] Prodromes are either entirely lacking or consist of sudden weakness malaise and muscular pains The onset is abrupt occurring frequently at night A patient going to bed apparently in good health may awake with a chill bathed in sweat and feeling deadly sick Precordial oppression a gripping dyspnea nausea and muscular cramps together with premonitions of death constitute acute attacks which follow each other rather frequently and in increasing strength At the height of such a paroxysm death may occur

The spleen is enlarged The urine secretion is small even to the degree of complete anuria Delirium is common The fever is usually high and remittent in type

The convalescence is slow and relapses may occur Immunity is not certain Mild cases occur but adults are more severely affected than children The pathological findings are unrevealing The content of the vesicles is not sweat but a serous exudate No specific therapy is known

Dermadromes —The outstanding symptom after which the disease has been named is the excessive *sweating* (Timmermann[394]) which in contrast to sweats in other fevers starts with the rising temperature and continues throughout the duration of the fever The sweating is so profuse that it is impossible to keep the patient even fairly dry by the most frequent changes of linen The sweat is supposed to have a musty odor After three to four days the characteristic rash appears However many patients die before reaching the exanthematic second stage of the infection The rash usually starts as a slightly papular eruption on the neck and chest and spreads in several crops over the whole body The forehead and scalp are heavily affected and the face the least[393]

The individual lesion is a red papule or macule with a central acuminate vesicle which is at first yellowish and clear but after one to two days is opaque The exanthem may at times especially in children be quite morbilliform but confluent scarlatiniform and hemorrhagic varieties have been seen in some epidemics[393] The vesicles dry and crust after two to three days and heal with a branny or flaky desquamation Oral lesions look like aphthae The eruption is preceded by formication or tingling and accompanied by a feeling of relief

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[392] Rousseau L La suette millaire dans le Montmorillonnais Bull Acad de méd Paris **113** 293 302 1935

[393] *Stroé A and Stroé H Die Kinderschweissfrieselkrankheit* Arch f Kinderh **95** 78 89 1931

[394] Timmermann H Der Schweissfriesel Vienna 1898 Alfred Hölder

Onyalai

Among the natives of West Central Africa occurs an acute febrile disease called onyalai, the main feature of which is a mucocutaneous eruption of hemorrhagic bullae. These lesions are usually found inside the cheek, on the tongue and on the palate, although bleeding may occur from all mucous membranes. There may also be localized hemorrhagic lesions of the skin. These blood blisters are umbilicated, trabeculated and filled with loosely coagulated blood. The disease may show all the features of a severe thrombocytopenic purpura.

Severe anemia, icterus, bronchopneumonia and central nervous system involvement are frequent. The mortality is high. There is profound thrombocytopenia with prolonged bleeding time, normal coagulation time, imperfect clot retraction and a positive tourniquet test. The intramuscular injection of whole blood is said to be a good method of treatment.[395]

Glandular Fever (Infectious Mononucleosis)

Glandular fever (E. Pfeiffer[396]) or infectious mononucleosis is a contagious febrile disease of unknown etiology, characterized by generalized lymphadenopathy, splenomegaly and lymphocytosis. The incubation period is usually seven days. The terms glandular fever or prolonged fever[397] of pharyngeal, anginose, thoracic, abdominal, nervous, septic and other types characterize the great variability of the disease. The prognosis is good.[85, 398, 399]

Dermadromes.—E. Pfeiffer[396] emphasized the absence of exanthems and Glanzmann[398] in his monograph on lymphemoid glandular fever elaborates on the lack of a characteristic rash. Other authors[399] however have occasionally or frequently[397, 400] seen erythema multiforme and lichenoid, morbilliform, diffuse erythematous, maculopapular, rose spot like or, very rarely, purpuric exanthems. The rashes appeared during the first two weeks.

The epidemic in London in 1930 was marked by unusually frequent typhoid-like rose spots which appeared before the lymphadenopathy. Recently a rash incidence of 14 per cent has been reported (Minkenhof after Robert[399]). The blood count remains indispensable for the diagnosis. Of importance is the velvety red appearance of the gums which bleed easily. In severe cases the teeth may submerge in these fragile tissues. On other parts of the oral mucosa, especially on the soft palate, small grouped papules may appear and cause a granulated appearance. On such infiltrations shallow, small or larger punched out, aphthous ulcerations may develop. Slight follicular and severe diphtheroid and

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395 Blackl W I Onyalai R Soc Trop Med & Hyg 25 207 2 6 193
396 Pfeiffer E Das Drüsenfieber Versammlung deutscher Naturforscher und Ärzte Köln 1889
397 Tidy H L Glandular Fever and Infectious Mononucleosis Lancet 1934 II 180 236
398 Glanzmann E Das lymphämoide Drüsenfieber New York 1930 S Karger
399 Lehndorff H and Schwarz E Das Drüsenfieber Erg d inn Med u Kinderh 42 77 85 1932
400 Rosalsky J F Jr The Skin Eruption and False Positive Wassermann in Infectious Mononucleosis (Glandular Fever) Internat Clin 2 39 1941

ulcerative tonsillitis have often been reported The oral ulcerations appear after the swelling of the submaxillary lymph nodes

Unilateral *conjunctivitis* of a dry granular character is not rare [399] In exanthematic cases the Wassermann and Kahn reactions may temporarily become positive [400]

Foot and Mouth Disease (Aphthous Fever)

Although the foot and mouth disea e (aphthous fever) is predominantly an epidemic infection of cattle and other cloven hoofed animals it is occasionally transferred to man by contact with infected animals or drinking of their milk The cause is a filtrable virus

In man the infection has an *incubation period of two days The on et is* sudden with fever headache and malaise On the following day salivation and an *eruption* of many umbilicated vesicles on the buccal and labial muco a appear the lesions being surrounded by a bright red areola The tongue and the pharynx may be similarly involved On the third or fourth day the di ea e enters a second stage [401] New grayish or yellowish vesicles and larger blisters with or without red areolae may cover the hands and feet and even the legs [402] The nail beds are often mentioned as the site of troublesome inflammations The nails may be shed or they may show transver al grooves Maculopapular multiform and varicelliform exanthems involving the entire skin or much of it have been described [403 404] The mouth condition together with diarrhea rhinitis and conjunctivitis and the symptoms of general infection may cause an alarming picture Around the fifth day the symptoms subside and after ten days or more the patient is usually cured [405] The prognosis is good although some deaths have been reported The treatment is symptomatic

The identity of human and animal infection has been corroborated by successful inoculation of human material into cattle[406] and guinea pigs [407 408]

Dengue Fever

Dengue fever is an acute nonfatal widely distributed febrile disease of the warm climates It is transmitted by various mosquitoes including *Aedes aegypti* the carrier of yellow fever The cause is a filtrable virus [409] The incubation period is about seven days [410]

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[401] Von Sch lt I Maul und Klau n uche beim M nschen Klin Wchn chr 1 630-63 1931

[402] Ariess L 2 Fäll von Maul und Klau n uche beim Mensch n Berl ti rärztl Wchnschr 37 231 19 1

[403] Gibbon A H A Ca e of F ot and Mouth Disease Lanc t 19 4 I 438

[404] Tapp in r S Maul und Klauens uch beim Mensch n Arch f D rmat u Syph 180 189 204 1940

[405] Gerlach Maul und Klau n euch b im M nsch n und Uebertragung auf Meerschweinchen Wi n klin Wchnschr 37 210 1924

[406] *Bertarelli* Uebertragung d r Maul und Klau n uch auf d n Menschen und Wied Impfung der menschlichen Krankheit auf die Rinder Ztl f Bakteriol 45 6 8 1907

[407] Waldmann O and Pape J Experim ntell Untersuchung n über Maul und Kla n euch Berl tierärztl Wchnschr 37 349 3 4 19 1

[408] Uhl nhuth I Uebertragung d r Maul und Klau n euche auf Me rschw inch n D utsch med Wchnschr 47 671-672 1921

[409] Simmons T S D ngu M Clin North America 27 808 8 1 1943

[410] Kl n r P and Lisansky E T Dengu Ann Int Med 20 41 51 1944

The disease starts with severe frontal headache and pain in the lower back in joints and in muscles Chills are marked and indolent lymphatic nodes are palpable over the posterior scalenus muscles[411] There is bradycardia in spite of the high fever, and leukopenia with a shift to the left The temperature falls to normal on the third day but fever often returns after one to two days (saddle back curve) The second fever is sometimes higher and ends by crisis around the seventh day Deaths are very rare but convalescence may drag out over several weeks No specific laboratory test nor treatment has been developed

Dermadromes—The initial fever is often (38 per cent, Simmons[409]) accompanied by an erythematous symmetric rash or extensive flushing which is most pronounced on the face, neck chest forearms and palms[41] The eyes are reddened also This flushing is out of proportion to the temperature and was seen in about 26 per cent of the cases during a recent major epidemic[410] The flushing subsides gradually If there was any erythema of the chest it may be converted into the secondary rash which does not involve the face This secondary or terminal exanthem was seen more often (37 per cent Kisner and Lisansky[410] 86 per cent Simmons[409]) It appears between the second and sixth days and is macular occasionally maculopapular scarlatiniform or rarely hemorrhagic It usually starts on the chest back or abdomen and spreads to the trunk but this sequence may be reversed if the rash starts later in the illness No definite relationship seems to exist between the onset of the second fever attack and the terminal rash which is followed by an imperfect desquamation and itching of the palms and soles[409]

Some authors emphasize the sweating and the variability of the rashes[413] Complicating pyodermatoses are common[414]

Pretibial fever An epidemic febrile illness of approximately five days duration characterized by slight respiratory symptoms headache leukopenia palpable spleen and a symmetrical maculopapular rash mainly over both pretibial areas vaguely resembling erythema nodosum has been observed among troops in South Carolina[415] The rash was present in 80 per cent of the forty cases All efforts to determine the nature of this pretibial fever were in vain

Phlebotomus Fever

Phlebotomus pappataci or sandfly fever is a benign sandfly borne virus infection of hot and dry countries characterized by a fever of two to four days duration severe frontal headache and eye ache photophobia and muscular pains There is leukopenia and shift to the left The face is described as curi

411 Stewart F H D ngue U S Nav M Bull 42 1233 1476 1944

412 Anigstein L Yellow Fe r and D gu J Pediat 22 612 617 1943

413 Misaizu H Beobachtung n b i einer Epidemie on D ngue Fi be mit mannigfaltigen Symptom n Acta d mat 20 85-86 193 Zbl 45 1

414 Dracoulides N Ob ations d rmatologiqu s au c urs de la dengue (penda t la pandémie d Ath nes en 19 8) Bull Soc franç d dermat t syph 36 612-615 19 9

415 Daniels W B and Gr unan H A Pretibial Fever an Obscur Di a e J A M A 122 361 1943

ously red and puffy in contrast to the body[416,417] and may stay so for weeks after the fever The conjunctivae are red and there is photophobia Crops of vesicles at the junction of the hard and soft palates[416] (not seen by other observers) and probably only in a minority of the cases purpuric scarlatiniform morbilliform urticarial and erythema multiforme like evanescent rashes[417] and perifollicular erythema in the axillae and about the elbows and knees have been mentioned Herpes is not a feature[418,419] but occurs occasionally[417] in severe and atypical fashion

Bullous reactions and severe edema following sandfly bites after convalescence are interpreted as allergic reactions[417]

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[416] Walker A S and Dods L Epidemic of Sandfly Fever in Palestine During 1940 M J Australia 28 345 349 1941

[417] Marchionini A Haut und Schleimhaut rsch inungen b im Pappatacifieb r in Anatolien Arch f Dermat u Syph 182 613-651 1942

[418] Schilling C Pappatacifieber Handbuch der inneren Medi in vol I Berlin 19 5 Julius Springer

[419] Sabin A B Philip C B and Paul J R Phlebotomu (Pappataci or Sandfly) Fever J A M A 125 693 700 1944

CHAPTER V

SYSTEMIC INFECTIONS

Varicella (Chicken Pox)

In 1931 Tezner[420] in a comprehensive review of the subject stated that the causative agent of varicella (chicken pox) has often been searched for and almost as often found This is a witty overstatement We know that it is a dermatropic probably filtrable virus related to but not identical with Paschen s elementary bodies which cause variola and vaccinia Injection of the content of the vesicular lesions of chicken pox into the rabbit s cornea produces within twenty four hours a small vesicle which bursts after seventy two hours The microscopic picture of the cornea is quite characteristic, especially the giant cells with large eosinophile inclusions found by Gins (see Tezner[420]) Tyzzer (after Lipschutz[421]) found nuclear inclusions which Lipschutz[421,422] believed to be microscopically identical with the inclusions found in herpes zoster (zoster bodies)

The virus is contained in the skin lesions and probably in the blood stream Experimental skin infection with nasal mucus has been as unsuccessful as the infection of the tonsils with vesicular fluid but the intradermal inoculation of blister serum produce after nine days a typical vesicle which always remains localized and can be successfully u ed for further inoculations The inoculation is unsuccessful in persons who have had varicella It immunizes against chicken pox with considerable reliability[423]

Droplet infection through the lungs eems to be the most important way of contagion indirect transfer is negligible

Chicken pox is endemic and epidemic usually affecting children Varicella has a good prognosis unless one of the rare complications occurs Newborn infants and adults are much less frequently but usually more severely af fected[424,425] The infection is followed by long lasting immunity

The incubation period varies from seven to twenty six days but is usually thirteen to fourteen days Prodromes are little marked Fever is common especially in older children or adults and convulsions sleepiness photophobia and gastrointestinal symptoms may occur Very short lived prodromal or initial rashes are not common (1 per cent) They are mostly scarlatiniform rarely

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420 Tezner O Varicellen Ergebn d inn Med u Kinderh 41 363 5 2 1931

421 Lipschütz B Die Einschlusskrankheiten der Haut Handb d H u Gk 2 1 164 193?

422 Lipschütz B and Kundratitz K Ueber die Aetiologie des Zoster und über seine Beziehungen zu Varicellen Wien klin Wchnschr 38 499 03 19 5

423 Greenthal R M Prophylaxis of Varicella With Vesicle Fluid Am J Dis Child 31 851 855 19 6

424 Waring J J Neuburger K and Geever E F Chickenpox Severe Form in Adults Arch Int Med 69 384-408 194?

425 Nebe Karl Ueber Varicella bei Erwachsenen Leipzig 1931 Dissertation

morbilliform or polymorphic and seem to forecast a more severe course Giant cell formation in the tonsils similar to that seen in measles has been found in chicken pox during the prodromal stage[46] All symptoms may be absent and the exanthem may break out with the patient in apparently good health This *conspicuous* lack of sick feeling often causes the child with varicella to be brought to the office of the dermatologist because the idea of a systemic infection does not enter the mother s mind This rarely happens in the other important exanthematic diseases of children



Fig 43 —Varicella (Courtesy Dr Max Fox)

Dermadromes —The eruption starts on the face and on the scalp that on the body (back) being only slightly later though some isolated vesicles may precede the main eruption The distribution of the exanthem which may develop fully in one to two days is most dense on *the trunk* and *becomes lighter toward the extremities* and the acra This *centripetal* tendency is in marked contrast to the centrifugal distribution of the variola pustules which leave the trunk and especially the abdomen relatively free and crowd on the hands and feet The individual lesion appears as a small *macule* which in twenty four hours *develops into a clear vesicle which is often surrounded by a relatively wide bright* red areola The blister is sometimes oblong rarely pustular or hemorrhagic Pri

[46] Tomlin on T H Chick npox Giant C ll Form in Prodromal Stage Am J Path 15 5 3 526 1939

mary umbilication of the filled lesions is rare though early rupture depression and formation of a sunken crust in the center may suggest umbilication but should not be taken as such The vesicle is multilocular, but the septa as well as the wall are much thinner than in small pox so that the lesion often can be wiped off with a rough towel The blister is quickly followed by a crust which



Fig 44 —Bullous and hemorrhagic chickenpox (Courtesy of Division of Dermatology Department of Medicine University of Chicago)

may adhere for many days or as long as two weeks A few larger and deeper lesions may leave pitted scars with pigmented margins but the marks are rarely disfiguring The lesions are more numerous on irritated or macerated skin The exanthems vary in density from a few lesions to a copious eruption of many hundreds of efflorescences in all stages of development This latter peculiarity is due to the appearance of successive crops and to the fact that the individual lesion may become arrested in any stage of development The crops may be

accompanied by mild fever After one week the crops stop appearing although miliaria like weak eruptions may continue to follow The last eruptions are mild and the lesions usually fail to mature to vesicles

There are several *clinical varieties* of chicken pox and its complications 4 0 4,7 The eruption may form bullous impetiginous or coalescent lesions Confluence indicates a severe infection



Fig 45 —Varicella gangrenosa Fatal case (Courtesy Dr Max Fox)

Varicella pemphigoides is a rare variety characterized by large flaccid bullae with adherent centers Such cases may be accompanied by high spiking temperatures[353] and have repeatedly taken a fatal course [illegible] Some of these cases seem to be a combination of varicella and secondary pyogenic infection Erysipelas is a dangerous complication *In some cases the vesicles remain very small this is called miliaria varicellosa*

In *varicella gangrenosa* the normally fast sequence of drying and crusting of the vesicles is disturbed by a progressive necrosis which leads to punched out gangrenous ulcers The floor of these ulcers is covered with necrotic greenish material *Hemorrhagic features are common so that the ulcers often appear* black However an occasional black discoloration of the otherwise normal crusts does not warrant the diagnosis of gangrenous chicken pox Several ulcers may coalesce so that palm sized gangrenous defects ensue which may even lay bare the underlying muscles In some instances the gangrene started in apparently normal skin and not from the vesicles

[illegible] Ronaldson, C. W., and Kellerher, W. H. Chickenpox: Anomalous Form, Brit. J. Child. Dis. 25: [illegible] 36 1928

[illegible] Schwartzman, J. Varicella and Pemphigus Acutus, Arch. Pediat. 57: [illegible] 98 1940

Gangrenous varicella is a severe disease with high temperature prostration and often fatal course Infants and sick youngsters are more likely to develop this complication than older and otherwise healthy children Scarlet fever diphtheria and tuberculosis are among the predisposing diseases Banks and McCartney,[429] in a fulminating case of massive skin gangrene in the eruptive stage of varicella found streptococci to be the causative organism Hemolytic streptococci are also the cause of dangerous cellulitis and of erysipelas and lymphadenitis Infected lymph nodes usually break down and form abscesses Cutaneous complications amount to 57 per cent of all the complications of chicken pox[430] The incidence of gangrenous varicella amounts to about 1 per cent[429] but seems to be much smaller in the United States More than one half of the reported cases of gangrenous varicella ended fatally



Fig 46 —Hemorrhagic and unusually copious varicella (Courtesy Dr Max Fox)

Knoepfelmacher[431] separates from other *purpuric* manifestations *in varicella* the prodromal purpura and the purpura which occurs not too infrequently in mixed infection of pertussis and varicella The varicella eruption is rarely hemorrhagic from the start The vesicle content may become bloody or there may be other purpuric features the whole syndrome of thrombocytopenic purpura[432] may develop during or after the infection in rare instances together

[429] Banks H S and McCartney J E Varicella Gangrenosa Due to Streptococcus Pyogenes Lancet 1937 II 311 314

[430] Bullowa J G M and Wishik S M Complication of Varicella Their Occurrence Among 2,534 Patients Am J Dis Child 49 [illegible] 1935 193

[431] Knoepfelmacher Varicellen und Hautblutungen Wien med Wchnschr 1916 p 990

[432] Cohen H J Acute Thrombocytopenic Purpura Following Varicella Arch Pediat 53 [illegible] 776 1936

with massive skin gangrene.[433] Pyogenic sepsis has been blamed in some of these cases.[430]

The diagnosis of chicken pox is only difficult in unusual types, in isolated cases, or in times of a smallpox epidemic. Many authors discuss the differential diagnosis of chicken pox and smallpox[434, 435] (Tieche after Tezner[430]). The most important points are: In chicken pox as compared with smallpox, the prodromes, especially fever, are mild or lacking. The distribution of the rash is centripetal, starting and massed on the trunk. It appears in crops and the lesions show *different stages of maturity. The lesion is generally less round and less firm* so that it can be wiped off, and it is rarely umbilicated. The halo (corona) is more irregular, wider, and it develops faster. These criteria should all be taken with a grain of salt, and the diagnosis should not rest on any one sign or symptom. (See also under Variola.)

No specific laboratory test for chicken pox has come into general use, so that a negative Paul's test for smallpox may in certain cases become an important diagnostic aid.

Occasionally *Kaposi's varicelliform eruption*, a rare acute vesiculopustular eruption with severe systemic reactions, may have to be considered. In most of the known cases the rash was superimposed on atopic dermatitis. The umbilicated lesions resemble vaccinia more than varicella, but they appear in crops and the Paul test is negative. There is increasing evidence that the disease is a generalized herpes infection.[436-439]

Herpes Zoster and Varicella

As far back as 1891 Von Bokay[440] published reports of five different instances of chicken pox in children following herpes zoster in a parent or other contact after a period approximately equal to the incubation period of varicella. These observations, apparently easy to check, were almost ignored until in 1909 the same author[440] presented a second series. Since then far more than 300 cases have become known and the puzzling matter continues to appear in additional publications.[441, 442] The most common type of relationship between the two diseases is an outbreak of varicella in one or several persons who have had con-

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[433] Stoesser, A. V., and Lockwood, W. W.: Varicella Complicated With Thrombocytopenic Purpura and Gangren, J. Pediat. 12: 641-647, 1938.

[434] Wesselhoft, C.: Differential Diagnosis of Chickenpox and Smallpox, New England J. Med. 230: 15-19, 1944.

[435] Laidlaw, F. W.: Smallpox and Chickenpox, Differential Diagnosis, New York State J. Med. 28: 310-312, 1928.

[436] Blattner, R. J., Heys, F. M., and Harrison, M. L. I.: Etiology of Kaposi's Varicelliform Eruption, J. Pediat. 27: 207-, 15, 1945.

[437] Lynch, F. C.: Kaposi's Varicelliform Eruption, Arch. Dermat. & Syph. 51: 1 9 137, 1945.

[438] Lane, G. W., and Herold, W. C.: Kaposi's Varicelliform Eruption, Arch. Dermat. & Syph. 50: 396-404, 1944.

[439] Evans, C. H., Bolin, V. S., and Steves, R. J.: Kaposi's Varicelliform Eruption, Arch. Dermat. & Syph. 51: 134-135, 1945.

[440] von Bókay, J.: Über den aetiologischen Zusammenhang der Varicellen mit gewissen Fällen von Herpes Zoster, Wien. klin. Wchnschr. 1909, p. 1323; Jahrb. f. Kinderh. 105: 8-3, 1924.

[441] Blatt, M. L., Zeldes, M., and Stein, A. F.: Chickenpox Following Contact With Herpes Zoster; 2 minor epidemics, J. Lab. & Clin. Med. 25: 951-955, 1940.

[442] Baker, L. P.: Generalized Herpes Zoster (9 cases), Arch. Dermat. & Syph. 40: 974-986, 1939.

tact with a person suffering from herpes zoster In several instances accidental chicken pox infection from other sources could be fairly conclusively ruled out for example in Lynch's[443] case by the fact that the hospital where the case occurred was in quarantine for twenty one days because of scarlet fever while the incubation period of chicken pox rarely exceeds seventeen days Occasionally



Fig 47 —Herpes zoster in varicella (Courtesy of Division of Dermatology Department of Medicine University of Chicago)

secondary cases of varicella developed from those varicella cases which stemmed from herpes zoster thus proving their true chicken pox nature However these infections did not prove as highly contagious as is usual [443 444] The appearance of herpes zoster after contact with chicken pox is seven times rarer than chicken

[443] Lynch F W Herpes Zoster and Chickenpox Arch Dermat & Syph 44 68-69 1941
[444] Monticelli M Herpes Zoster varicella Bull Soc ital pediat 3 183 188 1934

pox after zoster[440] Very rare too are the sequences chicken pox—herpes zoster—chicken pox or zoster—zoster—chicken pox or other alternations Chicken pox simultaneously with or following herpes zoster in the same person usually an elderly man, varicella with herpetiform groups of vesicles and herpes zoster with aberrant or generalized lesions have been reported[445] The cases in which



Fig 48 —Varicella in adult with herpes zoster Same patient as in Fig 47 (Courtesy of Division of Dermatology Department of Medicine University of Chicago)

one disease followed the other have been interpreted in favor of a close relationship or identity of the diseases[446] as well as to prove their different nature since immunity which probably follows herpes zoster and certainly follows varicella would be more likely to prevent the sequence than to produce it[447] The interpretation of the relationship between herpes zoster and varicella as a fortuitous one is refuted by the apparent lack of any co occurrence between for example herpes zoster and measles which should occur just as often if coincidence were the only factor The most interesting experimental study was made by K

445Fleming J Herp and Varic lla Simultan ou ly in Sam Patient Gla gow M J 132 7 73 1939

446Ferriman D C Chickenpox and H p s Zo ter in Sam Patient Lanc t 1939 I 930-931

447Schönfeld W Herpes Zost r und H rpes Simpl x Handb d H u Ck 7 1 1 12? 19 8

Kundratitz [448] who in seventeen out of twenty eight cases successfully inoculated herpes zoster into children who had not had chicken pox Two of the inoculated children developed after the varicella incubation period a generalized eruption identical with varicella The inoculation was never successful in children who had had chicken pox and those children who had been successfully inoculated with herpes zoster or who had been treated with zoster convalescent serum proved to be immune to varicella Lipschutz[4 1 4] found nuclear inclusion bodies



Fig 49 —Chickenpox a d herpes oster Th chickenpox p eceded the e uption by a few days (From Top F ankli H Handbook of Commu icable Diseases The C V Mo by Company)

which he believed to be characteristic of both diseases in the inoculation reactions of Kundratitz s[448] cases Kundratitz s experiments were on the whole confirmed by Bruusgaard [449] Experimental infection with varicella stemming from herpes zoster just by placing the beds of the children close together was accomplished several times by Bra lavskij [450] A new contribution is the finding of similar inflammatory changes in the spinal ganglia in varicella as are known to occur in

[4] Kun lratitz K Exp rim nt ll I be tragung on H rpes Zo ter auf d n M enschen und die B ziehung n on H rj Zo t r zu Variz ll n Monatschr f I I de h 29 516 23 19.5
[449] Bruusgaard E Th Mutual Relati n B twe n Zo t r and Varic lla B It J D rmat 44 1 24 103
[450] Braslavskij P H rpes Zo t r and Va icella. Kiev med Z Nr 3 and 4 43 53 1930 Zbl 38 351

herpes zoster[451] Some authors believe that the incidence curve of herpes zoster and varicella runs parallel

All theoretical explanations of the relationship between herpes zoster and varicella have so far remained unsatisfactory[4 0,452 45] mainly because of varicella zoster cases in the same person Unitarian and dualistic schools of thought have formed ranging from complete denial of any relation to close relationship with dermatropism of the virus in varicella and neurotropism in zoster The matter is still highly controversial[453] however some relationship cannot be doubted

Vaccinia

Vaccinia is an infection of cattle caused by a virus which seems to be identical with that of variola Animal passage probably has modified the infection in many respects It almost always causes a characteristic pustule at the site of infection followed only in extremely rare instances by generalized eruptions

The disease leaves the patient immune to vaccinia and smallpox Spontaneous infections with vaccinia are quite rare and occur mostly in dairy personnel The intentionally produced infection with vaccinia however is one of the most common and widely studied infectious diseases of the civilized world Though produced in order to attain a systemic effect that is immunity against variola vaccinia is usually not thought of as a systemic infection

The first three to four days after inoculation is the symptomless incubation period On the fourth day a raised papule (papilla) with a narrow red halo (aula) appears On the sixth or seventh day the papule changes into an umbilicated vesicle surrounded by a wide areola Between the eighth and tenth days the infection is at its height and often accompanied by lymphadenopathy fever and leukocytosis According to some authors the spleen is palpable for a short while The involution of the pustules starts on the eleventh day Three to four weeks after the vaccination the local process has wound up with a scar

The apparently solid papule appears histologically to be a vesicle with many chambers There are characteristic vacuolizations of the cytoplasm characterized by Unna[140] as ballooning and reticular degenerations The first term was chosen because of the vacuolization which finally leaves the prickle cells looking like bags filled with balls the nuclei The epithelial and other cells of the vesicles contain the variola vaccinia virus Inoculation of the vesicle content into the cornea of the rabbit (Paul s test) produces in thirty six hours characteristic epithelial papules with central crateriform necrosis The microscopic examination demonstrates many Guarnieri bodies[454] Paschen s elementary bodies can be demonstrated in smears from early lesions by staining They resemble cocci but they are smaller

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[451] Balogh E V Zur Entstehungsweise d Windpockeneruptionen (Ein Beitrag zur Frage Varicellen und Nervensystem) Verh 9 internat Kong Dermat 2 232 241 1936

[4] Nohara F J Beobachtungen von Zoster gleichzeitig mit Varizellenausschlag bei demselben Kranken Dermatologica 79 29-43 1939

[452] Bessau C Kummer I Nägeli O Bill J H and Schönfeld W Beziehungen zwischen Zoster und Varicellen Dermat Wchnschr 103 I 209 214

[454] Paschen F Vaccine and Vaccineausschlag Handb d H u G k 2 161 297 103

A great number of investigations have shown that the vaccinia virus enters the blood stream and appears in the air passages in almost all the organs[455] and in the secretions for example the urine[456]

The blood of vaccinated children without any complications may, from the third to the tenth day produce typical vaccinia in nonvaccinated children (H and K Herzberg after Paschen)[4 4]

Dermadromes —In spite of the generalization of the virus which probably occurs in all cases hematogenous skin infection and development of typical lesions are extremely rare These lesions must be separated from accidentally inoculated vaccinia on eczematous skin on the lips on the eyes or on other susceptible parts



Fig 50 —Vaccinal rash (Courtesy Dr Max Fox)

of the surface (eczema vaccinatum) True *generalized vaccinia* appears possibly after the third day but usually during the second week after the vaccination as a papular rash which passes through vesicular and pustular phases though not with the precision of the inoculated vaccinia The eruption is disseminated sometimes universal Exanthems are known Sometimes the neighborhood of the original vaccination for example the same arm is especially involved The content of the pustules produces characteristic lesions in the rabbit cornea and in the skin of nonvaccinated persons The eruption is accompanied by moderate

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[455] Gins H A Hackenthal H and Kamentzewa Natalie Neue Erfahrungen und Versuche über die Generalisierung des Vakzinevirus Centralbl f Bakteriol 110 115-119 1929 Experimentelle Untersuchungen über die Generalisierung des Vaccinevirus beim Menschen und Versuchstier Ztschr f Hyg u Infektionskr 110 4 9-441 1929

[456] Wollnitza Über Vaccina generalisata und Nachweis des Virus im Urin Zbl 87 487-458

fever and splenomegaly The differentiation from variola and varicella may be of practical consequence In contrast to smallpox there are no severe prodromes and no initial rash There is no drop in temperature following the eruption The acme is reached at the time of pustulation and is followed by slow lysis The pustules have no areola they are larger and they heal without scars (Drago after Paschen[454]) Severe varioliform cases with fatal outcome have been described [457 458 459] The microscopic picture in Shortt s[458] case was that of



Fig 51 —Hemorrhagic and eternally generalized vaccinia (Courtesy Dr Ma Fox)

vaccinia Corresponding changes were found in focal lesions of the spleen and liver [460] A pemphigoid eruption of the fetus after vaccination of the mother may occur [461]

Morbilliform urticarial bullous or rarely erythema multiforme like exanthems occasionally appear during the second week rarely earlier

[457] Anders Allg Kuhpocken mit tötlich Au gang Zt hr f Hyg u Inf ktion kr 88 116 1919
[458] Shortt O T de V r Ca of (n rali ed Vaccinia Lane t 1933 I 0- 81
[459] Melkhann C F and Ross R A G n ralized Vaccinia and Ec ma Vaccinatum M Clin North Am rica 2 785 1938
[460] Ross R A Virus and Rickett ial Di a es Cambridg Mas 1940 Harvard Univ rsity Press
[461] Lynch F W Dermatologic Con litions of the F t With Particular R ferenc to Variola and Vaccinia Arch Dermat & Syph 26 997 1019 1932

These eruptions may be analogous to the initial rashes in variola The postvaccinal rashes have rarely been seen after revaccination[46] The cause of postvaccinal rashes as well as of true generalized vaccinia is thought to be a disturbance of the antibody formation Normally these substances are produced in sufficient quantities to neutralize the virus in the blood stream so that no exanthem appears In other cases enough of the blood borne virus reaches the skin to cause an erythema In the papulovesicular generalized vaccinia, the antibodies are so weak or they appear so late that the virus deposited in the skin can complete a fairly normal development (Czerny and Opiz after Groth[463 464])

Hemorrhagic vaccinia and purpura after vaccination are very rare[465 466 467] (Voigt after Paschen[454]) The pustules are black and they bleed there are signs and symptoms of thrombopenic purpura The prognosis seems favorable

Some authors claim that the number and quality of the cars of the first vaccination indicate the degree of immunity which has been reached (Gregory after Paschen[454]) [468] In spite of great numbers of observations in revaccinated children no consensus has been reached Armstrong[469] found that out of seventy one ca es of postvaccination encephalitis in America eventy followed vaccina tion with one scratch only It is conceivable that too little skin reaction may not produce sufficient immunity to protect against such complications

Psoriasis may either develop at the site of the pustules or increased psoriatic activity and spreading may follow While the localized eruption can be inter preted as a Koebner phenomenon (provocation of psoriasis by local irritation) the flare up and generalization of psoriasis is well known to occur after many infections

The relation of so called *milkers nodules* on the hands of dairy personnel to true vaccinia is controversial[464 470 475] Vaccination does not seem to immunize against milkers nodules (Nagel after Robert[360]) Rashes similar to postvaccinal eruptions have been observed[4 6] in milkers nodules

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[462] Serefis S Polymorphes E anth m al Komplikation eine akzident llen Vak ination Dermat Ztsch 60 200 265 1931

Groth A Vaccina gen rali ata Zbl f d ge Hyg 16 865 867 19 8

[4]6 Croth A Zur Aetiologie der M lke knot n München med Wchnsch 76 2128 2130 19 9

[465] Paschen E Fall von Purpura im Anschlu s an die Impfung München med Wchnschr 1907 p 1801

[466] Heaton T C Purpura Associated With Vaccination Canad M A J 43 593 594 1940

[467] Schwartz A B Po tvaccinal Purpura Case Am J Dis Child 30 856 858 1925

[468] Stadler H Die Impfna b n als Indikatoren der Immunität g g n Variola und Vakzine Veröffentl a d Geb d Med V rwalt 42 363-404 1934

[469] Armstrong Charle Postvaccination Encephalitis With Special Ref renc to Prevention Pub Health Rep 47 1553 1568 1932

[470] Oppenh im M and Fessl r A Ueb r Melkerknoten Arch f D rmat u Syph 159 334-342 1930

[4] Schultze W and Crundh rr F J Ueber Melkerknot n mit toxischem F anthem Arch f D rm t u Syph 158 1 15 19 9

[472] Volgov A and Morozov M Histology of Milker s Nodes Sovet e tnik n rcol i de mat 9 338-353 1931 Zbl 39 289

[4] Stark A M and oth rs U ber di Pockenätiologi der og M lk rknoten Arch f D rmat u Syph 170 38 60 1934

[4] Woring r F Deux nou aux cas de tubercules du tray ur Bull Soc franç d dermat et yph 41 19 203 1934

[4] Pomuss B J Ueb r Melk rknot n Dermat Wchnschr 98 134 14 1934

[4] Kren O Melkerkn t n mit Exanth m Wien klin Wchnschr 2 1581 1930

Variola (Smallpox)

Smallpox is an extremely contagious usually epidemic disease It is caused by a virus in many points identical with that of vaccinia [454, 477] As in vaccinia the agent is contained in the cellular inclusions found in the lesions (see vaccinia) The characteristic inclusions Guarnieri s bodies can be demonstrated in the small *grayish ulcerated papule which develops after inoculation into the rabbit s* cornea (Paul s test) The disease is probably contagious even in the initial stages The virus is spread by contact droplets dust or contaminated persons and objects The crusts of the healing lesions are highly contagious as are the bodies of persons who have died from the disease Air and sunshine destroys the germs which otherwise are able to survive for a long time The disease con fers immunity although occasional reinfections have been reported Almost all persons who neither have had smallpox nor have been vaccinated during the preceding ten years are susceptible The fetus may become infected and be born with an exanthem or with scars

The *incubation* period is twelve days with some variations and it is a rule that the shorter the incubation the severer the course Thus in hemorrhagic smallpox the incubation period is often only eight days while in the mild variola minor the incubation period may be twenty one days [434] The *onset* of the disease is abrupt The patient is severely ill with high temperature frontal headache and intense lumbar and other muscular pain Vomiting and constipation may be present Delirium is common The skin is flushed and hot Women often start to menstruate at the outbreak of variola sometimes before the expected day Most authors agree that severe prodromes do not necessarily usher in a severe eruption although a mild initial stage is usually followed by a mild course

Dermadromes —A peculiarity of the prodromal phase of variola is the *initial rash* which is observed in 15 30 per cent of the cases It most often develops on the second day and is morbilliform or scarlatiniform rarely urti carial The morbilliform rash starts on the face and travels within a few hours over the body and especially over the extremities It is most often recognizable on the sides of the body on the extensor surfaces of the extremities [478] and on the mammae It vanishes as quickly as it appears Some authors[479] believe that the purely macular non petechial rash is of favorable prognostic significance but this is not always true [478] More importance is given to the much rarer scarla tiniform rash In this variety which may be seen on the very first day of the prodromes the abdomen below the navel and the inner thighs are flaming red Within this somewhat triangular shaped area (Simon s thigh triangle) petechiae *can frequently be demonstrated*

In some instances similar erythemas may appear on the shoulders and on the inner aspects of the upper arms They may be more dense on the vaccinated arm if not too much time has elapsed since the successful vaccination [478] This *erythema variolosum* vanishes relatively slowly It may still be seen in the early

[477] Haagen F Ätiologie der Pocken Arb R Gesundhamt 68 149-163 1933
[478] Tsurumi M and Kono S The Initial Exanthem of Smallpox J Infect Dis 29 109 113 1921
[479] Morawitz C Variola Handb d II u Ch 14 1 443 453 1930

eruption period and it has often been said that the sites of the initial erythema either remain free of pocks or have relatively few The petechiae seen in the initial rash should not be confused with the rare purpura variolosa

The end of the third day marks the end of the initial stage and the beginning of the decisive *eruptive period*

The *variola exanthem* appears first on the face and head Within three days it invades the trunk and then the extremities The face is usually the most densely covered part Areas subject to friction as the garter and belt areas or skin which has been irritated by iodine or other irritants or the macerated folds of the groin may produce a richer crop of lesions Face extremities and trunk in the order named show decreasing degrees of density The abdomen is the

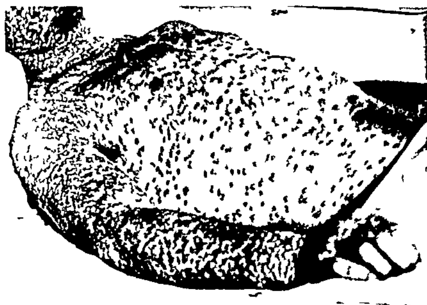


Fig 52 —Smallpox ninth day Severe case with confluent rash in the face (Courtesy Dr Max Fox)

least affected region However all these degrees are relative and vary widely with the severity of the case

The individual lesion which is accompanied by a slight burning or itching begins as a pinhead sized papule which grows to a bright red lentil or split pea sized efflorescence within one to two days On the third day of its existence the papule develops a small vesicle on its center which within two more days extends over the whole lesion Its content changes on the fifth day from the initial clear serum to an opalescent fluid and finally to frank pus on the sixth day (ninth day of the disease) This marks the beginning of the pustular stage The content of the vesicle is under considerable pressure often giving the palpating finger a firm shotty sensation This feature however has been overemphasized and it may be entirely absent [434] It is not possible to relieve the pressure by needle

puncture, since the vesicle is multilocular. The center of many lesions becomes navel like while the edge appears raised. The pustules are surrounded by a bright red narrow halo. The skin between the pustules is often swollen.

The outbreak of the variola exanthem is accompanied by a sudden drop in temperature after which the patient feels greatly relieved. In mild cases the temperature continues to fall throughout the eruption while in the more severe cases the temperature rises again with or even before the pustulation. The maturation of the pustules takes place in the order of their appearance so that the face is always one step ahead. The duration and the severity of the pustular stage varies. While in some cases the small number and the short lifetime of the pustules may affect the general condition but little, a copious or confluent



Fig 53.—Confluent smallpox. (Courtesy Dr Watson Campbell and Dr C S Newman from Sutton and Sutton, Diseases of the Skin, The C V Mosby Company.)

exanthem causes great suffering with recurrence of high temperature and delirium and all the possible complications of a highly toxic and septicemic state. Skin gangrene not related to bed sores has occasionally been observed. Most of the deaths occur in the suppurative stage. While the widespread inflammation of the skin naturally makes the patient most uncomfortable, much of his suffering comes from the *mucosal* eruptions. The mucosal efflorescence follows the same pattern as the skin lesions, papules, vesicles, pustules. However, the roof of the vesicles is destroyed early so that instead of the pustule an erosion develops. The mouth, the nasopharynx, the larynx and even the trachea down to the bifurcation may be affected. The tonsils become ulcerated by confluent lesions. The tongue is often relatively little involved. The discomfort of the patient is not so much caused by the actual smallpox lesions on the mucosae as by the diffuse catarrhal inflammation which accompanies the enanthem. This is particularly true of the nose and nasopharynx, which often are obstructed by bloody crusts

The conjunctiva bulbi is only rarely involved the conjunctiva palpebralis a little more often. Pustules may appear usually in small numbers in the vagina the rectum and the urethra.

The pustular stage at the middle of the second week represents the acme if the disease takes a normal course. From then on the edema of the face subsides and the pus at first in the facial lesions and then in the others in the order of their appearance becomes thicker and the areolae lighter. The pustules which were firm and shotty become flat and shrink. They form yellow crusts which finally become brown dry and loose. The pain subsides however a very annoying pruritus frequently accompanies the loosening and shedding of the scabs. The respiratory irritation subsides and at the end of the second week the temperature is again normal this time to stay. The healing pustules leave pigmentations and pitted scars of varying degree. The scarring may consist of a few pockmarks not much more severe than in some cases of varicella or it may disfigure the patient s face to the utmost for the rest of his life. Diffuse alopecia follows variola probably more often than it follows other exanthematic diseases. The hair grows back except in the few spots where pustules have destroyed the hair papillae.

The clinical picture of smallpox varies considerably with the epidemic and with the status of immunity of the patient. In addition complications may modify the course decisively.

In *variola confluens* as compared with variola discreta the pustules are so dense that they coalesce and form large superficial abscesses and infiltrations. All symptoms are aggravated. The face is most severely involved the trunk less so. The eyes cannot be opened the lips and the nose are swollen and crusty and the saliva runs from the mouth. According to an old clinical experience (Sydenham after Osler Christian[85]) the number of pustules on the face decides the outcome and a relatively mild eruption on the rest of the body does not make up for a dense and confluent exanthem on the face. Such confluent cases are sometimes but not always heralded by severe lumbar pain in the initial stage and by a precipitate eruption on the second or third day.

Variola minor is a mild form of variola with a sparse exanthem which does not always start on the face.[490] There is no initial rash and no second fever period. All symptoms run a mitigated and abbreviated course. Tièche[491] often observed a one to two day period without symptoms between the prodromes and the eruption. Very experienced authors believe that variola minor is a separate disease but others[492] propose a unitarian theory. Some of the arguments follow. No certain case of variola major stemming from contact with variola minor is known. Vaccination does not afford the same protection against variola minor as against variola major[493] although this is controversial.[494]

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490 Immermann H Variola Vienna 1896 Alfred Hölder

491 Tièche M Epidemiologische und experimentelle Studien über Variola und Vaccine Korresp Schweiz Ärzte 1913

492 Sobernheim G Variola und Alastrim Centralbl f Bakteriol 110 0 115 119 120 19 0

493 Van Campenhout E Considération sur le diagnostic de variola major et variola minor Bull Office internat d hyg pub 27 1738 1741 1935

494 Gröber F Beobachtungen bei einer Epidemie von Alastrim Deutsche med Wchnschr 60 793 94 1934

Variola minor does not always immunize against vaccinia (see Sobernheim) The variola minor pustule is white and has several times been described as unilocular and not umbilicated [48] Such terms as alastrim amaas kaffir pox white pox and Cuban itch have been used to designate the epidemic variola minor It should be emphasized that if the mild character of a case of variola is due to the status of immunity for example preceding vaccination infections stemming from such cases may be severe The exanthem may fail to appear after the prodromal symptoms Such cases of *variola sine exanthemae* are rare usually favorable but also contagious

Hemorrhagic complications may create two distinct varieties of smallpox If purpuric symptoms appear in the prodromal stage if the initial rash is purpuric or petechial or if the mucosae show early petechiae or bleeding one speaks of purpura variolosa or hemorrhagic smallpox These patients die within a few days in some instances before the outbreak of the exanthem Fulminating purpura discoloring wide areas may develop All who have seen such cases of black smallpox have been impressed by the ghastly appearance of the patient whose entire skin may be deep purple the face swollen the conjunctivae deep red and the gums bleeding

The term *variola pustulosa hemorrhagica* characterizes the cases with the appearance of hemorrhagic symptoms in the pustular stage This too is a severe and usually fatal complication At first the halos then the pustules themselves become hemorrhagic Osler[85] and other clinicians who have witnessed great epidemics of smallpox agree that the earlier the purpuric complications set in the more dangerous they are

The earlier clinicians[480] mention two rare peculiar cutaneous variation of the healing process Sometimes a warty looking crusty greasy mass may remain in the place of the pustule and only slowly become eliminated This is called wart pox *variola verrucosa* Still rarer is *variola siliquosa* Here the content of the pustules disappears rapidly leaving for a while an air filled blister The gross pathology of the inner organs shows a surprising paucity of changes The histopathology of the early stages of the variola papule shows acanthosis with vacuolization and liquefaction around a center in the higher strata of the prickle cell layer Here the multilocular vesicle develops The umbilication is caused by acantho is which raises the edges higher than the liquefied center The navel may disappear if the chambers of the vesicle coalesce or become more distended The peculiar cell changes described by Unna are identical with those in vaccinia (see under vaccinia)

The *diagnosis* is occasionally difficult A secondary syphilid may though rarely imitate variola and one should search for other syphilitic signs or symptoms Variola if modified by vaccination may resemble varicella However chicken pox has no prodromes and the temperature does not drop during the eruption which appears in several crops predominantly on the trunk The vesicle in varicella is very superficial and thin and can be wiped off while this is not possible with the deeper and more thickly walled smallpox lesion The areola (corona) in varicella is irregular and sometimes very wide while the halo around

the variola pustule is narrow and regular The shape of the varicella vesicle is often irregular even elongated in the body folds compared with the round circumference of the variola lesion Deep seated scabs on the palms are quite characteristic of smallpox The shotty feel of variola lesions may be absent and may occasionally even be found in varicella In smallpox the axilla often remains free while it is a favorite spot for the eruption of chicken pox.[465] Morawetz[139] mentions unusually copious eruptions of erythema multiforme as being a possible obstacle to the diagnosis Here the emphasis of the distribution is on the extensor surfaces of the extremities not on the face The prodromal stage the fever, the contacts the preceding vaccinations and especially Paul s test the scarification of a rabbit s cornea with a needle dipped into the questionable lesion establishes the diagnosis (see vaccinia) In persons who have been sensitized by often repeated vaccination a skin test with sterilized material from the questioned eruption may be positive within four hours (Tieche after Paschen[454]) if the disease is vaccinia or variola

No specific therapy is known The treatment is symptomatic Vaccination at the time of exposure attenuates the outbreak of variola to an attack of fever without eruption A few days after exposure vaccination can still weaken the course but this is no longer true after the outbreak of the prodromes

[5]Fall r A Differential Points in Diagno is of Smallpox and Ch ckenpox Ohio State M J 24 9 8 960 1928

Chapter VI

SYSTEMIC INFECTIONS

Pinta

Pinta (mal del pinto carate) is a tropical disease characterized by unusual pigmentary changes and caused by *Treponema carateum* This treponema was discovered by Grau Triana and Armenteros in Habana Cuba in 1938 The spirochete for which at least six names exist (Treponema herrejoni pictor americana pintae dischromeoderma) is demonstrable in active lesions by the dark field examination or by the same stains which are used to detect *Treponema pallidum* from which it is morphologically indistinguishable *For generations the disease was considered a mycosis However the absence of fungi the high incidence of positive Wassermann and Kahn reactions (Menck*[456] *60 per cent Herrejon and Pallares 100 per cent after Pardo Castello and Ferrer*[457] *and the rapid response* to antisyphilitic treatment made a spirochetal cause of the infection appear probable The disease is inoculable into normal and syphilitic persons but not into persons with pinta of the later stages (León y Blanco[458] Beerman[459]) It is believed that the infection takes place by contact and not by a vector No venereal transmissions have become known The infection conveys immunity The disease occurs predominantly among colored races in the Latin American countries About 600 000 sufferers are believed to live in Columbia and over 270 000 in Mexico[460] A few cases have been discovered among Negroes in Chicago[461]

Dermadromes —Mainly through the brilliant and heroic work of the Cuban dermatologists it is now known that seven to ten days after an inoculation of pinta material into the skin a minute *primary papule* with a red halo develops Within two months this initial lesion gradually becomes an erythematosquamous patch surrounded by satellite papules which tend to coalesce with the primary lesion The primary patch may grow slowly to 10 to 13 cm in diameter and finally become indistinguishable from secondary lesions (*pintids León y Blanco*[458])

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[456] Menck W Percentages of Positive Wassermann Reactions Associated with Various Diseases Fifteenth Annual Report of the Medical Department of the United Fruit Company New York 1926

[457] Pardo-Castello V and Ferrer I Pinta mal del pinto carate Arch Dermat & Syph 45 843-864 1942

[458] Leon y Blanco F Las discromias palmares y plantares en el mal del pinto Rev de med trop y parasitol bacteriol clin y lab 6 16 144 1940 Estudio epidemiológico del mal del pinto en una pequeña aldea del estado de Guerrero México, Rev de med trop y parasitol bacteriol clin y lab 6 189-200 1940 Las reacciones de Bordet Wassermann y de Kahn en el periodo secundario del mal del pinto Rev de med Trop y parasitol bacteriol clin y lab 6 201 0 1940 Nota sobre la evolución histórica de nuestros conocimientos acerca del mal del pinto o carate Rev de med trop y parasitol bacteriol clin y lab 6 259-30 1940

[459] Beerman H Pinta Etiology and Clinical Studies Am J M Sc 205 611-623 1943

[460] Fox H A Census of Mal del Pinto in Mexico Arch Dermat & Syph 31 227-229 1935

[461] Lieberthal E P Pinta in the Continental United States J A M A 123 619-621 1943

which appear five to twelve months or more after the infection A variety of pintids characterized as trichophytoid psoriasiform lichenoid and eczematoid have been described The lesions are at first pink then red purple and finally slate colored indicating the onset of the pigmentary changes which are so characteristic of the disease The older secondary lesions often show a depressed



Fig 54 —Pinta Typical triangular leukoderma of volar aspect of the wrists (From Pardo-Castello V Arch Dermat 1942)

center and an active raised margin. Coalescence of the lesions is a feature. The distribution becomes more and more symmetric and widespread and the pintids may involve any region, although they are found mostly on the exposed areas and over the bony prominences. There are hardly any subjective sensations. In Mexico the early secondary stages were called *empeines*. They were thought to be a separate entity. Their relation to pinta has only recently been elucidated by León y Blanco[498] (see Pardo Castello[497]).

The secondary stage gradually passes into the *tertiary* or *dyschromic* stage with the spectacular pigmentary symptoms which have given rise to the name mal del pinto (Spanish pintar, to paint, meaning piebald disease). The first dyschromic lesions may appear after one year, especially in symmetrical distribution on the hands, forearms, feet and lower legs. However, the face, the trunk and the scrotum may finally be covered with permanent vitiligo-like changes.



Fig. 55.—Pinta. Hyperkeratotic and dyschromic lesion of the palms. (From Pardo-Castello, Arch. Dermat., 1942.)

Especially characteristic is a depigmented area on the volar aspect of the wrist in the shape of a triangle with the base bordering the palm and the apex pointing toward the elbow. Such lesions are composed of irregular, sharply outlined spots of hyperpigmentation which in white persons, who are rarely affected, varies from yellow to brown and in colored persons from brown to slate blue and black, the center being white. Pardo-Castello[497] emphasizes the pepper and salt or mottled arrangement of the pigmented lesions. The discoloration may be found accompanied by follicular and diffuse keratoses and areas of atrophy.

The Wassermann is always positive in this stage The white patches represent the final stage and do not respond to antisyphilitic treatment which is effective in the other lesions

The general health seems little affected during this extremely chronic disease which may last several decades However it is likely that as in syphilis more internal manifestations will be discovered Already a high percentage of late cardio aortic lesions and spinal fluid changes have been reported [49]

The initial and secondary lesions show essentially the same *histological* changes that is edema of the rete and inflammatory infiltration The great dis turbance of the pigmentary physiology is expressed by the lack of pigment in the basal layer and great accumulations of melanophores in the cutis Spirochetes are numerous only in active lesions Late lesions become increasingly atrophic

The differential diagnosis includes syphilis yaws vitiligo leprosy and certain dyschromic conditions Seroreaction the finding of spirochetes and the effect of specific treatment will help However the differentiation from syphilis and yaws will rest mainly on the clinical appearance The effectiveness of the same treatment in all these diseases reduces the practical importance of the differential diagnosis

Frambesia (Yaws)

Frambesia is a tropical spirochetosis closely related to syphilis although different in many ways The word frambesia derived from the French framboise raspberry refers to the red papillomatous lesions which are a conspicuous feature The disease is called yaws in English le pian in French and la boubarole or boubas in the Caribbean area The causative agent is *Treponema pertenue* a spirochete which is morphologically indistinguishable from *Treponema pallidum* The in fection is endemic among the lower classes of all tropical countries the incidence depending upon the unsanitary conditions rather than on the race Contrary to a widely held belief that frambesia is predominantly a disease of the colored population it is certain that poor living conditions cause a high percentage of infections among the white population [493]

Transmission occurs chiefly by direct contact The fly Hippelates pallipes culex mosquitos or leeches possibly play roles as mechanical vectors Venereal contagion is extremely rare due to the infrequence of superficial mucosal lesions However penile primary lesions have been observed[494] and are even considered very common in the Cameroons [495] Congenital infection is questioned by many authors although claimed by some Infection with yaws seems to immunize against syphilis [496]

The *incubation* period lasts two to three weeks during which time mild febrile prodromes often occur

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[49] Saenz B Triana J and Armenteros J Pinta in Cuba Arch Dermat & Syph 41 463-479 1940

[493] Pardo-Castello V Frambesia 500 Cases Arch Dermat & Syph 40 762-775 1939

[494] Mayer M and Nauck E G Framboesie Handb d H u Gk 12 857 1932

[495] Hallenberger Framboesia Arch f Schiffs u Tropen Hyg 20 B (heft 3 1916

[496] Fox H Skin and Tropical Diseases New England J Med 231 48 -485 1944

Dermadromes —The *primary lesion* called the mother yaw appears usually on the exposed parts of the legs or much less frequently elsewhere The initial sore starts as a papule or pustule which soon becomes granulomatous or ulcerative Such lesions may disappear or become inconspicuous among the great number of almost identical secondary lesions In a considerable number of cases the primary lesion keeps on growing and develops slowly into an enormous destructive ulcer Such mother yaw lesions have been seen to remain active as long as twenty years They may heal with a scar in any stage or may extend peripherally and deeply even to destruction of the underlying bones [493]



Fig 6 —Yaws Early papulohyperkeratotic plantar lesions (From Pardo Castello V Arch Dermat 1939)

Multiple primary lesions and the appearance of satellite papules around the sore are well known

From six to nine weeks after the infection the *secondary eruption* appears This is a papular rash often ushered in by prodromal symptoms like fever muscular pains and headache There is a generalized lymphadenopathy (Baermann

after Mayer and Nauck[494]) The secondary exanthem has a peculiar tendency to develop luxuriant papillomatous lesions These efflorescences may be generalized grouped about the body orifices numerous or scanty small or large They may appear as miliary pin point sized elements as impetigo like crusty lesions or as raspberry like papillomatous granulomas [493 495] Most of the secondary lesions disappear but groups of papules arranged in rings (ringworm yaws) or in lichenoid plaques persist during the late secondary period The soles are often covered with symmetric deep cornlike painful papules which are surrounded by keratotic eczematoid scaly skin (crab yaws) (Fig 56) The truly granulomatous and frambesiform nature of such plantar lesions becomes evident after removal of the thick horny top layer [497] On the palms such lesions may look psoriasiform Areas of mottled pigmentation and depigmentation on the hands and feet may create a picture which closely resembles pinta[493] (Schuffner s picture in Mayer and Nauck[494])

The *tertiary* lesions are seen earlier than in syphilis A period of late secondary latency is rare As in syphilis the late lesions may be ulceroserpiginous sometimes of enormous size with a nodular border and a scarred center or deeply destructive and granulomatous They may destroy joints and bones and cause pathological fractures Particularly horrifying are the facial and naso pharyngeal mutilations known as *gangosa* which may cause complete loss of the nose and may extend to the lips and lay open the nasal and oral cavities Later on scarring may cause microstomia and the hands under similarly destructive and cicatrizing processes may become monstrously deformed and mutilated Pardo Castello[493] emphasizes the bone destructive tendency of yaws in contrast to the more osteoplastic nature of the corresponding syphilitic processes

There is remarkably little involvement of the mucous membranes Destruction of the soft palate is rare and cardio aortic and cerebrospinal changes are infrequent [493]

The pathology of yaws largely follows the pattern of syphilis The proliferative tendency of the papules which in syphilis manifests itself in the condylomata is much exaggerated in yaws

Yaws apparently renders the patient immune and there seems to be some degree of cross immunity in the later stages of syphilis and yaws

Treponema pertenue is demonstrable in many of the lesions and occasionally in the late gummatous processes which in syphilis is only extremely rarely the case Wassermann Kahn and the related reactions are positive in 100 per cent of the secondary cases less often in the later stages [496] The disease is inoculable into monkeys and like syphilis into the anterior chamber of the rabbit s eye and into the testicles of the rabbit

The treatment is largely the same as for syphilis with the emphasis on the arsphenamines and bismuth Mercury and iodine are reported to be unsatisfactory Oral arsenicals for example acetarsone are effective and convenient

[496] Schüffner W Die Spirochaeta pertenuis und das klinische Bild der Framboesia tropica München med Wchnschr p 1364 1907

under primitive conditions [493] The treatment consists of daily doses of 0 25 Gm for twenty days These courses are repeated several times after intervals of two weeks Penicillin has shown promising results [498]

Juxta-articular Nodes

Subcutaneous movable pea to walnut sized or occasionally much larger nodules of firm or hard consistency occur on the extensor and lateral surfaces of the elbows knees and other joints [499] They grow slowly for years usually sym



Fig 57 —Juxta a ticular nodes (Cou tesy of Divi ion of D rmatology D partm t of Me licine University of Chi ago)

metrically often multiple never in large numbers The lesions called juxta articular nodes are tender in the first years of their development but later are painless and stationary There is no tendency to ulcerate or to heal spon taneously The affected are as a rule elderly persons

[498] Whit hill and Austrian T eatm nt of Yaws With Penicillin Bull Johns Hopkins Hosp 75 23 240 1944

[499] Zakon S J and All n H S Juxta Arti ular Nodes Quart Bull Northwest rn Univ M School 14 2 0-273 1940

The *pathologic* picture [500] (Jeanselme after H Hoffmann[119]) is that of a cyst with a thick fibrous vascular outer wall in which perivascular inflammatory reactions with foreign body type giant cells and proliferation of blood vessels dominate Toward the center of the cyst the inflammation subsides the elastic fibers deteriorate and the nuclei lose their stain The center is a mass of hyalin or liquid degenerated material



Fig 58 —Syphilitic juxta articular nodes (From Kalz F Arch D rmat 1943)

The nodes are rare in temperate zones and common in the tropics This is due to the fact that the tropical treponemal diseases especially yaws [494] but also syphilis [119 500 501] pinta [473] and bejel [503] are apt to cause juxta articular nodes in their later stages Spirochetes were demonstrated regularly in the nodes of thirty six patients with frambesia [500 503 504] Patients with active lesions should receive antisyphilitic treatment

Besides the treponemal diseases several disorders particularly chronic arthritis may sometimes cause typical juxta articular nodes [119 111 505]

Relapsing Fever

A group of relapsing fevers is characterized by attacks of severe acute fever lasting two to ten days [15] The causative organism *Borrelia recurrentis* (*Spirochaeta obermeieri*) discovered in 1868 is a very large spirochete about six times the length of the diameter of a red blood cell and is found in great numbers in the blood during the attacks It is transmitted by lice bedbugs (Tictin after Eggebrecht[505]) and ticks [506] probably not by bite but by inoculation from the crushed infected insect body with the scratching nail There are a number of

[500] Jeanselme M Über syphilitische juxtaartikuläre Knotenbildungen Arch f Dermat u Syph 152 132 157 1926

[501] Kalz F and Newton D L Syphilitic Juxta Articular Nodules Arch Dermat & Syph 48 6 5 1943

[502] Hudson E H Yaws and Syphilis Am J Trop Med 21 545-55 1941

[503] Van Dyk and Oudendaal In H ne Histology and Cause of Juxta Articular Nodes Geneesk tijdschr v Nederl Indië 82 419 1942

[504] Arzvisky A and Bulvachter A Symbiotic Infection and Syphilitic Juxta-Articular Nodes Sovet Vestnik Dermat 9 41 56 1931 Zbl 39 443

[505] Eggebrecht E Fleckfieber Recurrens Vienna 1920 Alfred Hölder

[506] Schilling C Rückfallfieber in Handbuch der inneren Medizin Vol II Berlin 1925 Julius Springer

geographic varieties of relapsing fever differing in vector duration and number of attacks The relapsing fevers are important in Europe and Africa less so in America where there are some endemic foci in California and Nevada [507] The first attack starts abruptly after one to seven days of incubation There may be prostration often vomiting cough splenomegaly and increasing anemia The attack ends by crisis and the patient recovers remarkably quick but after one to two weeks he has another though often milder attack Such bouts may recur two three or even five times The prognosis is good the fatality rate in most epidemics is less than 5 per cent

Dermadromes —Dermadromes are inconspicuous and inconstant There is a decided icteric tendency which together with the increasing anemia may create a dirty grayish brown color This facial browning was emphasized by the older authors[505] (McCormack after Eggebrecht[505]) With varying frequency in different epidemics rose spots similar to those in typhoid morbilliform and very rarely scarlatiniform and miliary rashes[505] have been noticed The relapsing fever roseola is described[509] as appearing at the end of the first attack most frequently on the lateral surfaces of the trunk on the back on the extensor surfaces of the elbows and about the wrists Face and legs remain free The spots are smaller than those in typhoid round purely macular and pink to red in color They fade after about one hour but since they do not appear simultaneously these spots are visible for a much longer period The exceedingly ephemeral character of the spots is stressed by other authors [250] In ten years of experience with American relapsing fever in Nevada Parsons did not notice any rashes (personal communication)

Since the diagnosis rests on the finding of spirochetes in the blood the infrequent exanthems are *hardly of diagnostic importance The usual symptoms* accompanying profuse *sweats* sudamina and mild desquamation are common *Herpes* was noticed in up to 30 per cent of the cases in certain epidemics *Petechiae* (which should not be confused with flea bites) and other hemorrhagic symptoms especially nosebleed occur[250] occasionally especially at the end of the attack It is interesting that the acumen of the older clinicians did not fail to notice that patients with relapsing fever usually show the excoriations pigmentations and pyodermatic infections connected with chronic pediculo is and neglect a state known as *vagabond s skin*

Specific treatment consists of a few injections of arsphenamine

Weil s Disease (Leptospirosis ictero-hemorrhagica)

Weil s disease (Leptospirosis ictero hemorrhagica) is an acute spirochetal infection with fever gastrointestinal and hepatic symptoms and prostration After five to six days of high temperature a large percentage of the patients become jaundiced and hemorrhagic tendencies become manifest The mortality

[507] Morrison S h and Parsons L R lapsing F J A M A 116 220-221 1941
[508] Strong R P R lapsing Fever Cli North Am rica 27 731 744 1943
[509] O ttinger J and Halbrech J Eph mere Roseola beim Rückfallfi ber Münch n med Wchnschr 69 778-779 1922

amounts to about 12 per cent with most of the deaths occurring around the end of the second week

The causative spirochete is found in the blood

Dermadromes —Frequent skin manifestations include icterus and hemorrhagic lesions Scarlatiniform urticarial[510] and other types of rashes are rare Non angry endogenous bulbar conjunctivitis and episcleritis are considered early and striking symptoms[511]

There are *milder varieties of Leptospirosis* for example the so called inundation or mud fevers in Germany in which *morbilliform* rashes occur[511 512]

Ratbite Fever (Sodoku)

There exist two clinically similar diseases which develop in man after the bite of rats but which are attributed to different microorganisms One of these caused by *Streptobacillus moniliformis* has been discussed under the heading Haverhill fever Under the name of sodoku which in Japanese means poisoning by a rat the other has been known for centuries only in Japan although it is as cosmopolitan as the rat Simultaneous infection with both microorganisms occurs[513 514]

The cause of sodoku *Spirillum minus* (formerly *spirochaeta morsus muris*) was discovered in 1917[515] It is a fast moving spirochete having only two to five spirals and shorter in length than the diameter of a red blood cell There are flagella at both ends (B McDermott after Beeson[516])

A great number of cases with the spirillum present have been reported from many countries In a great number of the cases children were affected[517] Epidemics are not known The disease is rare one case being recorded among 20 000 hospital admissions in Kansas City Yet because of its wide use in the treatment of general paresis the symptomatology of the disease is well known

Spirillum minus is harbored by rats especially the vicious *rattus norvegicus* but also in a host of other rodents and occasionally by cats and dogs White mice and guinea pigs are susceptible to laboratory inoculation Animal inoculation with blood taken at the height of a febrile paroxysm is the most reliable method of demonstration[518] No pure cultures have been grown so far The organism may occasionally be demonstrated in the serum from a primary lesion in a local lymph node or in the blood[519] with the help of the dark field or with

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[510] Lorenz G Jr Studies in Weil s Disea U S Nav M Bull **42** 560 566 1944

[511] Lathe J Schlammfieber Erntefieber Wasserfieber Feldfieber Infektion durch Leptospiren Med Klin **35** 1133 1138 1939

Rimpau Feldfiebe Münch n med Wchn hr **85** 1977 1979 1938

[513] Nathan H Rattenbisserkrankung Zbl Chir pp 7 758 1933

[514] Anderson N P and Specto B I Rat Bite Fever Associated With Sporothrix J Infect Dis **60** 344-349 193

[515] Futaki I Takaki T Taniguchi T and Osumi S The Cau of Rat bit Fever J Exp Med **23** 49- 0 1916

[516] Beeson P B Rat bit Fev r Due to Spirillum Minus J A M A **123** 33 -334 1943

[517] Brüning H Sodoku (Rattenbisskrankheit) bei Kindern Ergebn d inn Med u Kinderh **44** 1-44 193

[518] Francis E Rat bite Fev nd Relapsing Fever i th U S A Tr A Am Physicians **47** 143 151 193

Rogliano A G Two Cases of Rat bite F er Surgery **21** 632-635 194

stains used for spirochetes *Inoculation of mice is more likely to yield results* than microscopic procedures although the accidental occurrence of spirochetes must be ruled out

The incubation period varies from two to thirty six days with the greatest frequency between seven and twenty one days[51] The outbreak of the disease is often preceded by malaise headaches loss of appetite and muscular pains

Dermadromes —The bite wound which is usually healed at the outbreak of the disease changes into a *primary lesion* which may become an indurated and *wide ulcer with steep edges necrotic floor and angry bluish red surroundings*[51 59] In some cases the primary chancre is marked only by a blister (Knowles and Das Gupta after Breinl[50]) or it may be absent The local lymph nodes are *swollen and tender Later generalized adenopathy* develops Acute high fever with chills accompanies the first attack which lasts several days and is almost regularly accompanied[51] by a rash It should be emphasized that in only 20 to 25 per cent of the cases of sodoku which were induced for treatment of general paresis did a *rash* develop[5] (Teitelbaum after Brown and Nunemaker[51]) This rash may start as a livid erythema around the infected wounds[53] and spread to other parts Erythema multiforme like papulo urticarial or macular rashes as well as (Taccone after Bruning[517]) livid *erythematous plaques* up to 14 cm in diameter with or without induration and sometimes with a pale center are common These lesions are usually not symmetrically distributed[517 54] (Knowles and Das Gupta after Breinl[50])

Petechial pustular and morbilliform *exanthems* in sparse or copious dissemination over the entire body only about the joints or in isolated areas have also been observed A papular eruption in the mouth may occur[55] A peculiar feature is an acute episode of *urticaria* which occurs shortly before the end of the attack (Miyake after Brown and Nunemaker[51]) Sometimes severe muscular pains nausea and vomiting dominate the picture Edema of the lower legs especially around large indurated plaques[54] is a frequent feature[56] and is considered to be of unfavorable prognostic significance Leukocytosis is marked Attacks with flare ups of the primary lesion as well as of the rash and the other symptoms may recur at intervals of about five days The number and severity of these relapses vary from six to ten or even more but the bouts generally become milder as immunity develops The relapsing character of the disease is not always evident since it may consist of prolonged periods of sustained or of daily intermittent fever producing a great variety of clinical pictures Without specific treatment the disease may pass into a chronic stage

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[50] Breinl F Die Rattenbisskrankheit Handb d H u G k 12, 1 399-418 193

[51] Veen H Rattenbisskrankheit Nederl Tijdschr v geneesk 75 608-613 1931 Zbl 37 632

[52] Hershfield H R S Kibl C S C R y S Ko lg M T S hmitt O R a l Saund rs A M Sodoku Treatment in Paresis J A M A 92 7 773 1929

[53] Kersten F Über Rattenbisskrankheit Hygiea 91 318 3 9 19 9 Zbl 32 73

[54] O Leary P A The Dermatologic Aspects of Rat bite Fever Arch Dermat & Syph 9 233 301 19 4

[55] Knudsen I Ein Fall von Rattenbissfieber (Sodoku) Ugeskr f laeg r 99 363 366 1937 Zbl 57 534

[56] Wolff H G Rat bite Fever Arch Dermat & Syph 25 3 7 4 193

In some cases severe sensory or motor nervous symptoms prevail Diffuse and patchy *alopecia* has occurred in later stages The hair grew back after general improvement[5 4]

The *Wassermann reaction* and related tests become positive in 50 to 60 per cent of the cases[3 1]

The mortality of the treated patients is low No fatality occurred among 125 cases reported in the United States

The clinical diagnosis must take into account a great many fevers although the history of a ratbite the primary lesion and the laboratory findings will secure the diagnosis The differentiation from rat bite transmitted Haverhill fever is made by the laboratory findings[3 0] as well as by the presence of arthritis and the lack of a pronounced primary chancre in Haverhill fever Haverhill fever after ratbite is probably more common than sodoku

Specific *treatment* consists of from three to ten injections of neoarsphenamine or similar arsenicals Bismuth is also effective[5 7] The first administration of specific drugs may be followed by a Herxheimer reaction[5 8] Recurrences have been seen after less than three injections

The *therapeutic inoculation* of the disea e into patients with general paresis instead of malaria was done in a great number of patients but has been aban doned because complications occurred and control of the infection often proved difficult

African Trypanosomiasis

The trypanosomiasis of central Africa (sleeping sickness)[5 9 530 531] is caused by the flagellates *Trypanosoma gambiense* and *Trypanosoma rhodesiense* These mi croorganisms are blood parasites of many wild and domesticated large mammals for example oxen sheep and antelopes and are transmitted to man by the bite of the tsetse fly *Glossina palpalis* The transmission is cyclical and mechanical The trypanosomes are most abundant in the blood during the febrile attacks but they are also found in the lymph nodes the cerebrospinal fluid and serous fluids They can be stained demonstrated by dark field and cultivated on salt agar (NNN medium)

The disease is endemic and at times epidemic in large parts of equatorial Africa especially around lakes and along rivers where the t et e fly lives At times the population of large areas is decimated by the disease which affects the colored races as well as the white The infecting bite is often immediately or within one week[53] followed by local inflammation These primary chancres do not develop invariably but furunculoid and ulcerative lesions with regional

[527] Ca t llani A Rat bite F er Proc Roy Soc Med **27** 157 1934

[528] Oz ki Y R tt nbi skrankheit Isoli rungsmethod des E reg rs Jap J D rmat & Urol **32** 46 193 Z t **42** 384

[529] Manson Bahr P H Manson s T opical Diseases Londo 19 9 Cass ll & Co Ltd

[530] I ll rsberg F R African Sleeping Sickness M Cli No th Am rica **27** 835-847 1943

[531] May M Haut rs heinu g n b i exotischen Krankheit n Trypa osomiasis Handb d H u Ch **12**, 1 180-185 1932

[532] Graf H Beitrag zur Pathologi des Glossi a palpalis-Sti hs und d r Inkubati nszeit bei S hlafkrankheit Arch f Schiffs- u Tropen Hyg **33** 210 2?? 19 9

lymphatic involvement fever and the local presence of the trypanosomes have been observed beyond doubt[5 9, 531, 53, 533] About two to three weeks after the infection the patient is stricken with fever of varying intensity and course the



Fig 59 — African trypanosomiasis Secondary exanthem (From L Owen courtesy The Annals of Tropical Medicine and Parasitology The University Press of Liverpool)

irregularity being a diagnostic feature[5 9] The patient becomes weak and anemic and his mental abilities suffer General lymphadenopathy is a constant though varying feature with the lymphatic nodes at first being soft later hard Head

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[5 9] Géry L R Les phénomènes cutanés au cours de la trypanosomiase humaine en particulier dans la race blanche Thèse de Paris 1910

aches paresthesias and a peculiar kind of deep hyperesthesia on knocking against a hard object known as Kerandel s sign indicate the early nervous in volvement

Dermadromes —The primary lesion has a deep red center surrounded by a pearly white vesicular zone and a red halo [53] Erythema and infiltration around the bite may persist far into the secondary stage The bite however differs in its appearance from the more transitory *secondary eruptions* [534,535] Characteristic of the early secondary stage but not present in all patients nor at all times [536] are *urticarial erythemas* in large round patches rings or crescents which have a decided tendency to spread peripherally and heal in the center Coalescing circinate rather large patterns may cover the entire back [533 537] These trypanids are of unpredictable and fugitive nature They may be without change for days or even several weeks and then they may evanesce quickly reappearing in other places The erythemas are slightly raised but not or little infiltrated [531 536] pink in color of normal temperature often sensitive and sometimes very itchy es pecially if they are of a more exudative papular type [536] Erythema nodosum occurs [5 9 533] The blood taken from lesions contains more trypano omes than the peripheral blood of the other skin The relatively delicate erythema is diffi cult to detect in colored skin * In some cases the erythema is annular and linear[538] like the erythema annulare encountered in rheumatic fever

Localized edema especially of the face is common in the secondary stage [533 534] Another dermadrome is a vascular bluish mottling independent of the erythemas (Master after Mayer[5 1])

The fading skin lesions do not leave any trace [536] The secondary stage may last a long time seven years usually being considered the maximum The skin manifestations become less marked and less frequent and gradually the disease drifts into the sleeping sickness stage with deep mental changes stupor and somnolence during daytime restlessness at night muscular twitchings tremor and convulsions Hepato splenomegaly is present If not treated death in profound cachexia is inevitable

During the *encephalitic* stage early features including erythema may still be present The gross pathology is meager Microscopically perivascular round cell infiltrations can be seen throughout the brain and especially in the erythema tous skin [536]

The *diagnosis* rests on the finding of trypanosomes in the blood in the lymph node material or in the spinal fluid The clinical diagnosis of trypanosomiasis

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D k ll r berger of the American Mission to Lepers who ha had an almo t unique experience with Afri an t ypanosomiasis does not beli e that th rash are v ry commonly seen si ce mo t of th pati nts in th t eatme t cent rs ha e adva ced ca s and th color t kin makes the erythemas difficult to obs r e (p rsonal commu ication)

[533] Ruge H Sleeping Sickne s Med Welt 13 1485-1488 1939

[534] Ch valli r P a d Lévy G Un cas le trypanides é uption précoc de la maladie de sommeil Bull Soc fra ç d dermat et syph 35 185 19 8

[535] Darré H Les Symptomes cut nés de la t ypanosomias humai Ann de dermat et syph 9 673 1908

[537] Owen D U Clinical Notes Trypa osomia is Ann T op Med 22 47 5? 19 8

[538] Audry C Eryth me an ulai c ntrifug et trypanosomias B ll Soc franç de dermat et syph 39 185-186 193

may be extremely difficult especially in persons who have moved from Africa to other countries The large erythemato urticarial centrifugal and annular erythemas are a most valuable sign Together with internal manifestations they are almost diagnostic Arsenic as tryparsamide pentamidine (M & B 800) and naphuride (Bayer 205 germanin) are considered of high value

American Trypanosomiasis (Chagas' Disease)

American trypanosomiasis is caused by *Trypanosoma cruzi* and transmitted from infected persons and reservoir animals (armadillo opossum) by various species of *Panstrongylus triatoma infestans* and other bugs



Fig 60 —Chaga dis ase Primary le ion (I culation chagoma fourteenth day) (Courtesy Mi ion de E tudios de Patologia Regional Argentina Jujuy Argenti a)

Skin Manifestations have long been considered of little importance Recently however Mazza and his associates[539 547] demonstrated their significance

[539] Mazza S and Fr i e R S Ma if ta io es utá as I I oculazion (Chagomas) y h matóg nas enf rmedad de Chaga Universidad Buenos Ayres Mi ión le E tu ilo d Fatologia Regio al Argentina (Jujuy) Pu bl a ion 46 pp 3 7 1940

[540] Ma za S a d Ure lay C Chagoma d Inoculazión s guido I es jui otripa i le morbiliform Ibid Pu bl 46 pp 58 84 1940

[541] Maz a S a d Miyara S Chagoma d inoculazion y es quizotripani le polimo fa Histopatologia Ibid Publ 46 pp 85-101 1940

[542] Ma za S Basso G Ba so R a l Conte D Chagoma anti ra qulal chag multiples metastaticos y hematog nos y compl jo oftalmoganglionar Ibid Publ 46 pp 105 118 1940

[543] Mazza S Basso G a d Ba so R Chagomas h matóg os Ibid Publ 48 1940

[544] Ma za S and Jörg M F Chagoma xperimental Ibid Publ 47 1940

[545] Mazza S and oth rs Investig io es nf med d d Chagas Ibid Publ 4 1940

[546] Mazza S Es quitripánl les ul ero as tar ilas n enf rmedad de Chagas y otras manifestaciones erup ivas Ibid Publ 71

[547] Mazza S and Aran la C A Fua ll v rauch bei I r am ika ischen Lei hmanios Arch f chiffs u Trop n Hyg 35 553 591 1931

in a series of important investigations A primary skin lesion may appear as a large dark red prominent and deeply infiltrated nodule with or without intact epidermis (inoculation Chagoma) which is histologically characterized by fat necrosis Lymphangitis follows the primary lesion The inoculation often occurs on the face especially about the eye Thus the first symptom often is a bipalpebral unilateral edema with conjunctival injection This eyelid edema lasts about four weeks (Romaña s sign)



Fig 61 —Chagas disease Unilateral and bipalpebral edema and conjunctivitis (Romaña s sign) About three weeks after infection (Courtesy Mision de Estudios de Patologia Regional Argentina Jujuy Argentina)



Fig 62 —Chagas disease Rash five days old (Courtesy Mision de Estudios de Patologia Regional Argentina Jujuy Argentina)

As early as five days after the infecting bite a papular rash in the neighborhood of the bite a generalized circinate morbilliform or scarlatiniform erythema and cutaneous and subcutaneous nodules some of large size have been observed These nodules are very firm and deep red if they arise from the more superficial strata Mazza also describes impetiginous and ulcerative eruptions seen several months after the infection



Fig 63 —Chagas disease Rash five days old (Courtesy Mision de Estudios de Patologia Regional Argentina Jujuy Argentina)

Since the thyroid is often affected in the later stages dermadromes which occur in myxedema may be encountered *Edema* of the face and skin and also *bronzing* are mentioned The South American authors consider treatment with Bayer 7602 of great value but the drug the formula of which is secret still lacks general recommendation because of the danger of nephritis [545]

A skin test with a cruzin has been developed * The diagnosis however rests mainly on the microscopic and cultural evidence of trypanosomes in the patient s blood

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* Mayer and Pifano Abstracted in Trop Dis Bull 39 90 1942

[545] Mackie Th T Hunter G W and Brookes Worth C A Manual of Tropical Medicine Philadelphia 1945 W B Saunders Company

Leishmaniasis

The leishmanias are flagellated protozoans which are capable of producing a group of diseases which are all of dermatological interest Two of them oriental sore and American leishmaniasis (espundia) and possibly a third disease tropical granuloma inguinale are predominantly skin diseases and therefore will not be discussed *Visceral leishmaniasis* or *Kala azar* however is an internal disease with specific skin manifestations It occurs in an infantile and in an adult form which are closely related

The causative protozoan is a small ovoid or round body found either free or in cells of the reticulo endothelial system particularly in the spleen the liver and the bone marrow In cultures on blood or salt agar (NNN medium) they assume the characteristics of flagellates and are inoculable into dogs and monkeys The disease is endemic in the Mediterranean and the Near and Middle East especially in India which has been visited by great epidemics Sandflies (Phlebotomus) are now considered as vectors with dogs as a reservoir particularly in the Mediterranean area



Fig 61 —Post kala azar dermal leishmaniasis in an incompletely treated case of visceral kala azar Depigmented nodules over the [illegible] (Courtesy Dr S K Ghosh Dastidar)

The incubation period is over ten days long latency may occur Mirzoian[349] claims to have found the primary lesion in inconspicuous lentil sized papules on the faces of children who several months later showed secondary symptoms of infantile kala azar The lesions which contain leishmanias may still be present at the time of the outbreak of systemic symptoms or they may have healed and left pigmented spots The onset is insidious or abrupt with spiking fever which

[349] Mirzoian N A Primary Lesions of Visceral Leishmaniasis in Children Trop Dis Bull 40 295-296 1943

may last many weeks Then an afebrile period with improvement may occur followed by a relapse of fever After several attacks a chronic state of emaciation low temperature and anemia becomes established Gradually the liver and spleen enlarge to tremendous size—the big protruding abdomen contrasting sadly with the thin limbs The appetite remains good for a remarkably long time Unusually low leukopenia and later ascites and edema are common Death is caused by cachexia or intercurrent disease for example dysentery or noma The microscopic *pathology* shows abundant leishmanias in the reticulo endothelial system

Dermadromes —The skin gradually takes on a claylike gray or dusky color especially on the hands and feet This mixture of pallor and pigmentation is seen in white as well as in colored races [531] The dusky color accounts for the

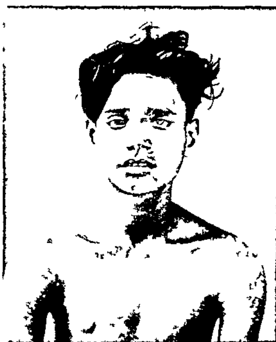


Fig 65



Fig 66

Fig 65 —Post kala azar dermal leishmaniasis in a person of dark complexion Small nodules on the partly depigmented areas on the chin from one of which Leishmania donovani could be demonstrated in the smear Sharply defined depigmented spots are scattered over the chest shoulders and face Patient had visceral kala azar one year ago and was treated with 7 Gm of ureastibamine which is much less than the therapeutic dose (Courtesy Dr S K Ghosh Dastidar)

Fig 66 —Noma as a complication of kala azar Sternal puncture smear showed Leishmania donovani (Courtesy Dr S K Ghosh Dastidar)

name kala azar meaning black fever Petechiae and other hemorrhagic lesions especially bleeding gums are common With the progressing cachexia small ulcerations about the elbows and knees and occasionally larger ulcerations along the legs may develop Specific papules and gangrenous ulcers containing leish

mania occur [550] as well as secondary cachectic ulcerations, such as noma. A most interesting cutaneous form of kala azar[551-553] has become known as the *post kala azar leishmanid*. Eighty per cent of the patients were known to have had kala azar and to have been treated with antimony. Of the rest (Napier after Mayer[531]) a previous kala azar infection could be assumed. The eruption starts with erythematous or depigmented patches on the face especially about the nose and mouth. Such macules resembling leprosy may later appear on the limbs and on the trunk (see colored illustrations in M. Mayer[531]) but the chin, the upper lip, and the eyebrow region are most frequently and most heavily involved. The macules are often followed by nodules which however may also appear first. These nodules are pea sized or a little larger, semiglobular, firm, nonulcerating and covered with atrophic skin. Their color at first is red, later becoming decidedly orange. They may coalesce and form ridges of tuberous lesions which resemble xanthoma tuberosum multiplex. The nodules contain only few leishmanias, mostly in giant cells in the center of a granuloma consisting mainly of macrophages and fibroblasts. The hypothesis has been advanced that some possibly antimony fast leishmanias remain in the skin and cause the local recurrences.

The *diagnosis* of kala azar may be suggested by the geographical location and the resistance of the fever to quinine. The finding of leishmanias by splenic or sternal puncture is diagnostic.

Kala azar is *treated* with antimony compounds. The post kala azar leishmanid does not respond well to this drug. It may become arrested in the late xanthomatoid form and remain without changing.

Malaria

There is no cutaneous lesion invariably or even frequently connected with malaria. Physicians of malaria free countries are inclined to visualize the malaria patient as having a sallow skin. This is only occasionally true. In countries where malaria occurs usually a high percentage of the population is infected and suffers from attacks. However the typical *malarial color*, a dirty yellowish brown sallow hue which in relatively rare instances may gradually take on deeper shades with a greenish component, is rare. The yellowish discoloration is more pronounced immediately after an attack and may approach a bronze shade as in blackwater fever.

Diffuse discoloration of the skin in malaria may be due to anemia, from the destruction of the erythrocytes, to icterus or to hyperpigmentation. Occasionally melanemia caused by large amounts of free malaria *pigment* in the blood serum may influence the skin color. The hyperpigmentation may compare with

[550] Shapiro, Y. M., and Btesh, S.: Kala Azar in Palestine. Case With Cutaneous Lesion, Tr. Roy. Soc. Trop. Med. & Hyg. 33: 57, 62, 1939.

[551] Acton, H. W., and Napier, L. E.: Post Kala Azar Dermal Leishmaniasis, Indian J. M. Research 15: 9, 106, 1927.

[552] Brahmachari, U. N.: A New Form of Cutaneous Leishmaniasis—Dermal Leishmanoid, Indian M. Gaz. 57: 125-127, 1922.

[553] Napier and collaborators: Post Kala Azar Dermal Leishmaniasis: A Series of Publications, Indian M. Gaz., 1929 and 1930.

addisonism in intensity and distribution including oral manifestations. Racial pigmentation of the gums can be ruled out by the effect of specific treatment which however removes malarial pigment deposits but slowly. Many authors have suggested that the adrenal cortex plays a part in the formation of the cutaneous pigment in malaria and there is some pathological evidence to support the clinical facts. F. Rosenthal and Lowenthal[554] found in such a case almost complete atrophy of the adrenals. Two types of pigment occur in the skin. The



Fig. 67. Malaria tropica: chloasma periorale and butterfly shaped pigmentation over the cheek. Similar pigmentation has been described in bilharziasis, ankylostomiasis and other conditions. (Courtesy Prof. A. Marchionini, Ankara, Turkey.)

specific *malarial pigment* (hemozoin) is derived from the destroyed red cells. It contains iron but because of its firm grasp on the iron atom does not give the ordinary Berlin blue (Potassium ferrocyanide and HCl) reaction. It is taken up by the reticulo-endothelial system discoloring mainly the spleen, liver and bone marrow and in extreme cases it may be found in the lumen of capillaries. The skin does not store the pigment; however it may be found in blood vessels

[554] Rosenthal, F., and Löwenthal, K.: Addisonid folg. Malaria, Zentralbl. f. Haut- u. Geschlechtskr. 34: 534, 1931.

Hemosiderin occurs be ides the malaria pigment Skin pigmentations in malaria may also be caused by *melanin*[555] Chloasma like spots on the face are not rare These sometimes occur[56] as the peculiar mustache shaped variety called chloasma periorale[55] which like many dermato es of the lips leaves a thin white border

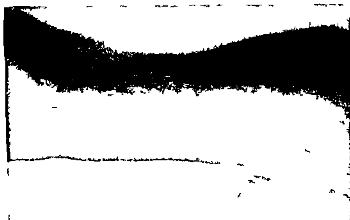


Fig 68 — Malaria tropica morbilliform rash (Courtesy Prof A Marchionini Ankara Turkey)



Fig 69 Gangren in mala ia tropi a (Courtesy P of A Ma chionini Ankara Turkey)

line between it and the vermilion area Sometimes the pigmentations in malaria are pellagroid in di tribution being found over the dorsa of the hands and the knuckles

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[555] Kaufma E Di pathologis h n Pigm tierung n d r Haut in I rer Medizin Neurologie und P y hiatri H ndb d Haut u Gk 4 ? 1011 1 ?1 1933

[56] Marchio ini A M lari Cuta eous Ch ges Clinical Study Acta d mat venerol 21 93-348 1940

[57] Pof F V Durch Fu ktionsstörungen des w iblichen G ital ystem he org rufene Hauter krankung n D rmat Wchnschr 82 ?93 19 6

addisonism in intensity and distribution including oral manifestations. Racial pigmentation of the gums can be ruled out by the effect of specific treatment, which however removes malarial pigment deposits but slowly. Many authors have suggested that the adrenal cortex plays a part in the formation of the cutaneous pigment in malaria and there is some pathological evidence to support the clinical facts. F. Rosenthal and Lowenthal[554] found in such a case almost complete atrophy of the adrenals. Two types of pigment occur in the skin. The



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[554] Rosenthal, F. and Löwenthal, K.: Addison infolge Malaria, Zentralbl. f. Haut u. Geschlechtskr. 24: 534, 1931.

relapses of chronic malaria in up to 30 per cent of their cases In malaria countries it seems good advice to look for the parasites in cases of chronic and unexplained urticaria or even to try quinine as a diagnostic test

Petechiae purpura and other *hemorrhagic* symptoms have often been reported In some of these cases[563] it could be shown that the petechiae were caused by arterial or capillary *thrombi* and vascular wall infiltration *Plasmodia* could be demonstrated in the lesions Circulatory disturbances of the hands and feet may cause painful sensations of heat as well as other paresthesias

Gangrene of circumscribed areas with or without Raynaud like symptoms and sometimes necessitating amputation is on record in a considerable number of cases [531 556 564 565] It is probably caused by endarteritis In the course of chronic malaria occasional dermadromes may occur due to the severe anemia (for example coilonychia[556]) The resistance to secondary infections is decidedly lowered Leishmaniasis cutaneous diphtheria and other secondary infections may take an unusual course The most spectacular secondary infection is *noma* A Eckstein[566] (in Turkey) found malaria in nineteen out of twenty two cases The patients were mostly small boys There is a striking parallel between the incidence of noma and the malaria mortality, in seasonal as well as in regional respects [556]

Noma (Cancrum Oris, Stomatitis Gangrenosa)

Noma is a rare disease in western civilization Eckstein[566] saw only one case in ten years of service at the Du seldorf Children s Clinic while he observed no less than forty cases during three years in the Children s Hospital at Ankara Turkey Similar experiences have been reported from China Epidemics of noma were observed in former years in European hospitals Almost exclusively a disease of childhood noma is predominantly a nonspecific complication of acute infectious diseases Measles typhoid [567] congenital syphilis [568] and particularly malaria[566] are known to create the conditions in which the peculiar gangrene of the cheek occurs Agranulocytosis and acute leukemia are other predisposing diseases [569 570] Some cases without known preceding disease have occurred

The clinical picture shows a gangrenous stomatitis which *sometimes in a* fulminating manner breaks through the cheek and upper lip and destroys all tissues including the bone and teeth which lie in its path Then the well known *horrible destruction of one cheek* surrounding the nose results The lesion is

[563] Braue L and F aenk l F Da Malariaexanthem im klinis h n und pathologi ch anatom Bil le Ar h f Sch ff u Tr p Hyg 25 355-363 19 1

[564] Dor S E Cutaneous Aff tio In V ious Dis as Brit J De mat 18 418 1906

[565] Leo F Ga gr of Feet in A ut Larvate Pe ni ious Mal ia Ar l ed atti d Soc Ital di chir 41 1045 1051 1938

[566] E k t in A Stom titis Ga grenosa Am J Dis Child 59 219 237 1940

[567] Lsh r S J an l Ros D E A C of Canc um Ori Followi g Typhoid F v r With Plastic R pair Can d M A J 25 446-449 1931

[568] Baltz W N ma Ba l 1937 Disse tati n

[569] S if rt F Zu Kra kh itsauffassung d r Noma und gl ichartig r Fo m n des Gewebsbrandes Zentralbl f Chi 65 1858 1863 1938

[570] Ml k n F I fectious Ga gr n of th Skin Du to Ba t rial Synergi m Arch Surg 31 253 1935

decidedly unilateral causes little or no pain and temperature and even appetite are much closer to normal than one would expect a surprising observation which can also be made in the final stages of destructive oral cancers

There is no strong leukocytic reaction [566] Only in the late stages does general toxemia develop The post mortem examination reveals necrotic and degenerative liver and spleen changes The mortality as based on 175 cases from the literature is 95 per cent Eckstein [566] after switching from neoarsphenamine which proved disappointing to antigangrene serum in large doses locally intramuscularly and intravenously had more than 50 per cent recoveries in twenty one cases

Although there is no complete agreement about the cause it is assumed by most authors that Plaut Vincent s symbiosis of fusiform bacilli and spirillae plays an important part These microorganisms have frequently though not always [571] been found in the lesion and in the surrounding apparently normal tissues [566]

Amebiasis Cutis

Ulcerations of the skin caused by *Endamoeba histolytica* occur in amebiasis either in connection with an operative abdominal wound or around the anus or without direct connection with the infected viscera for example on the glans penis The amebic ulcers[57] are rapidly spreading lesions Varying activity in different portions of the margin causes an irregular jagged outline The edge is undermined purulent and surrounded by a red halo The floor is covered with indolent granulations and pus The skin lesions respond to emetine

[571] Friedmann J L b Noma der Wange Schweiz med Wchnschr 1930 I 61 63
[572] Engman M F J and Meleney H E Amebiasis Cutis (Endamoeba histolytica) Arch Dermat & Syph 24 1 1 1931

Chapter VII

SYSTEMIC INFECTIONS

Rickettsial Diseases

Rickettsial diseases of man and many animals are caused by gramnegative, coccoid or bacillary intracellular microorganisms which are usually borne by arthropods especially lice and ticks and which need tissue containing media for successful culture With the exception of the rickettsiae of the otherwise different Q fever they are not filtrable [573] The serum of patients with rickettsial diseases agglutinates specifically certain strains of *Bacillus proteus* (Weil Felix reaction) The clinical appearance of the rickettsioses of the typhus group is best illustrated by its most important representative typhus itself from which the others differ but little

Typhus Fever

Typhus fever (typhus exanthematicus) is a severe endemic and epidemic disease the importance of which for the human race equals that of plague and cholera [574] It has accompanied most of the wars and famines and other up heavels of history Its victims in Ireland during the early decades of the nine teenth century numbered millions The epidemic form is possibly with a few exceptions spread by body lice After an incubation period of thirteen to four teen days the patient suddenly develops fever chills severe headaches and pros tration The fever is continuous ending by rapid lysis after approximately two weeks Temporary mental disturbances during the fever and insomnia are common The attack is followed by a long period of convalescence which may last two or three months The attack is characterized by a rash stupor low blood pressure tender and enlarged spleen (denied by Gordon[575]) and various gastrointestinal and renal symptoms The loss of weight is very marked [576] The blood shows a shift to the left and thrombocytopenia which may reach 100 000 during the fifth to eleventh days [577] The mortality rates vary widely Children and groups who have been exposed for a long time to infestation with lice are often only mildly ill In people beyond 50 years of age in the under nourished and in newcomers from disease free countries who are not accustomed to body lice for example physicians and nurses the disease is apt to take a more severe course with mortality rates higher than 50 per cent

[573] Dyer R F The Rickettsial Diseases J A M A 124 1165 1944
[574] Zinsser H Rats Lice and History New York 193 Little Brown & Company
[575] Gordon D M Brill Disease J Michigan M Soc 39 653-655 1940
[576] Virus and Rickettsial Diseases Harvard University Press Cambridge Mass 1940 article by J F Gordon pp 8 8 871
[577] Schittenhelm A Das Fleckfieber Handb d inn Medizin 1 645-6 8 19 5

The gross pathology is unrevealing but the severity of the systemic infection is shown by typical widespread microscopic vascular lesions in the central nervous system the heart and especially the skin



Fig 7 Typhus lesion on the second day of exanthem Swelling of the endothelial cells and well defined perivascular cellular reaction (Courtesy Woodward Th E and Bland E F J A M A)

The infection conveys lasting immunity

The diagnosis is based on the clinical picture the epidemiologic conditions and the Weil Felix reaction Sometimes complement fixation tests and biopsy of a skin lesion are useful

Dermadromes —The importance of the rash is reflected in the various names of the disease such as spotted fever typhus exanthematicus Fleckfieber fièvre exanthématique Murchison (after Curschmann[578]) collected nineteen different terms referring to the rash

In the first two days of the fever an *initial exanthem* consisting of a few $1/2$ mm wide petechial papules on the trunk can sometimes be observed[579] The initial exanthem may occasionally be morbilliform or urticarial[577]

[578] Curschmann H Das Fleckfieber Nothnagel Spezielle Pathologie u Therapie Vol III Wien 1900 Alfred Hölder

[579] Lipschütz B Die Klinik des Fleckfieberexanthems Arch f Dermat u Syph 126 414 557 1919

The main rash appears most often on the fourth to sixth day of the fever rarely as early as the second or as late as the ninth day[580] The eruption is often preceded by a characteristic drop in temperature In the early stages before it becomes plainly visible the rash can be demonstrated by a warm bath or a tourniquet[581] The most comprehensive dermatological evaluation of the rash has been given by Lipschutz[579] This article contains excellent illustrations

The rash appears continuously and not in a series of crops so that the definite number of spots is reached within one or two days[5 8] The eruption begins on the upper abdomen and chest then in rapid succession spreads to the back and to the extremities The armpits and the inner surfaces of the upper arms are the places to look first for spots[55] The fully developed rash may be extremely copious with the greatest density on the trunk From the trunk to the acra and to the face the density decreases on the whole with some accentuation on the dorsa pedum which is in contrast to the scarcity of lesions on the thighs and lower legs Eruption on the palms and soles is not the rule The exanthem starts with pale ill defined pinhead to lentil sized hardly palpable often irregular maculae which as soon as they have reached a few millimeters in size no longer fade completely under glass pressure Confluence of neighboring lesions into irregular and slightly raised spots occurs The color is not bright red but has an increasingly brownish tinge This indicates the *hemorrhagic component* which manifests itself in more or less numerous petechiae within and between the spots The purpuric phenomena are a measure of the severity of the infection[5] Purpuric lesions are often found in the folds and on the back In the mature stage which is reached around the twelfth day the color is decidedly purplish and a delicately bluish marbled vascular pattern may be seen between the lesions which is easier to recognize from a short distance in moderately bright light The old physicians called this subcuticular mottling or mulberry rash (Buchanan and W Jenner after Baumler and Aschoff[583]) After the twelfth day the exanthem fades leaving yellowish brown pigmentation which may persist for a while A slight branny desquamation which can be provoked by gentle rubbing takes place during and some days after the fading[584]

In up to 20 per cent of the cases varying with the epidemics no exanthem could be observed A macular erythema is occasionally seen on the buccal mucosa It precedes the exanthem Initial conjunctivitis is common Herpes is rare The nails often register the severe disease by a white transverse line (Botkin and Pletnew after Schittenheim[577]) Pletnew[580] saw longitudinal *fluted* lines

The *micropathology* of the lesions has been studied by F Fraenkel[585] and Bäumler and Aschoff[583] There are foci of hyaline degeneration necrosis and

[580] Pletnew D Flecktyphus Moskau Epidemie 1917 19 0 Ztschr f klin Med 92 298-301 19
[581] Pusch Klinisch und serologische Beobachtungen bei Fleckfieber Veröff a d Geb d Mediz Verw 14 111 1 8 1 1
[582] Dyer R E Typhus M Clin North America 27 7 5-789 1943
[583] Bäumler C and Aschoff L Fleckfieber Med Klin 11 95-99 1915
[584] Delamare G Note sur la desquamation furfuracée dans le typhus exanthématique Bull Acad de méd 86 306 30 19
[585] Fraenkel E Zur pathologischen Anatomie des Fleckfiebers München med Wchnschr 68 969 971 1921

endothelial proliferation in the intima of the small arteries and precapillaries These lesions form protruding intravascular buds and may give rise to small thrombi In the endothelial cells rickettsias have been found in small numbers[586] Furthermore there is a perivascular infiltration of *lymphocytes plasma cells* and epithelioid cells which resemble adventitial histiocytes These changes are found in the papillary vessels of the skin and especially throughout the brain and heart

No specific treatment is known A prophylactic vaccine is available

A mild variety of typhus known as Brill's[587] disease endemic or murine typhus with a mortality rate of less than 4 per cent is endemic in the east and southeast of the United States and in many ocean harbors The disease is harbored by rats and transmitted by rat fleas and rat lice[53] The exanthem was seen in 64 per cent of 115 cases[588] appearing about the fifth day starting on the trunk and spreading centrifugally rarely reaching the face and palms There often were only a few maculopapular lesions of 2 to 5 mm in diameter

Rocky Mountain Spotted Fever

Much more dangerous than endemic typhus is Rocky Mountain spotted fever *Approximately 600 cases occur every year in the west and 200 additional* cases in the remainder of the United States The average mortality is $12\frac{1}{2}$ per cent This rickettsiosis is caused by Rickettsia rickettsii and transmitted by various ticks[589] The clinical picture resembles typhus closely A mottled initial rash has often been seen to appear with the fever thus preceding the exanthem[590] which breaks out between the second and sixth days of the illness It is rarely seen below the elbows and knees or on the face[591]

The rather copious rash is like the typhus eruption at first maculopapular and red especially in the evening later it is petechial and even frankly purpuric especially in severe cases The rash is followed by desquamation and pigmentation The individual lesion measures 2 to 4 mm in diameter[591] The rash may be extremely profuse[592] with hardly any normal skin left or it may be very sparse and even completely absent It may appear in successive crops[593] Hemorrhagic factors may cause the usually discrete lesions to coalesce into purpuric areas which may involve the entire body Gangrene of the soft areas like the scrotum or the soft palate may occur[590 593 594] In abundant eruptions the skin is very tender The distribution is a little different from typhus in that the rash most often[595] appears first on the flexor surfaces of the wrists[591] and ankles

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[586] Sikl H Rickettsia in Exanthemknötchen ... hämorrhagischem Fleckfieber Časopis lékařů českých 60 61 6 1921 711 1 17

[587] Brill N E An Acute Infectious Disease of Unknown Origin Am J M Sc 139 484 0 1910

[588] Stuart B M and Pullen R L Endemic (Murine) Typhus Fever Ann Int Med 23 ... 0 36 194

[589] Parker R R Rocky Mountain Spotted Fever J A M A 110 118 1 3 1938

[590] Anikstein L Spotted Fever Problem Clinics 2 890 913 1943

[591] Topping N H Rocky Mountain Spotted Fever M Clin North America 27 722 733 1943

[592] Floyd M L Rocky Mountain Spotted Fever J Iowa M Soc 27 291 96 1937

[593] Baker G F Rocky Mountain Spotted Fever 0 Year Study of Wyoming Cases Journal Lancet 63 70 13 1943

[594] Baker G F Rocky Mountain Spotted Fever Ann Int M 1 17 17 2 1 194

[595] Ong H A and Raffetto J F Rocky Mountain Spotted Fever J Pediat 17 617 6 3 1940



Fig 73 Pocky Mountain sp tt d f ver Sev r a co nplicated by exfoliative d rmatiti Not n be td d tick in the skin of th eck an l arms (Courtesy Dr l F Bak)

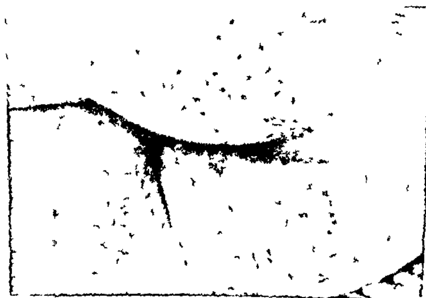


Fig 4 Rocky M u n j f (u t y D R R Ba ker L S Public Health Service Rocky M unt in Laboratory)

spreading centripetally from there within two days [593] to the back the arms the legs and the chest and finally to the abdomen, where it is least pronounced Palms soles and face are involved last [573] There is some relief of the muscular aches and pains after complete eruption

Fig 75

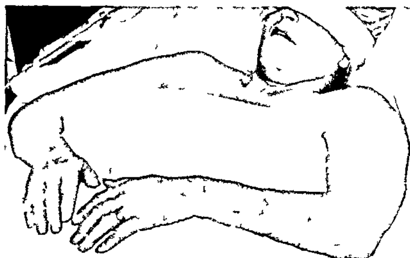




Fig 76

Fig 75 —Rocky Mountain spotted f v r Ra h i p techial an l of c trifugal distril ution Acm (Court y Dr (E Baker)

Fig 6 —Rocky Mountain spotted feve Not great d nsity toward th foot a l purpuric spots on the thigh Acm (C o t sy D G F Baker)



Fig 77 —Rocky Mountain spotted fever Dense rash on the hands (Courtesy Dr G E Baker)

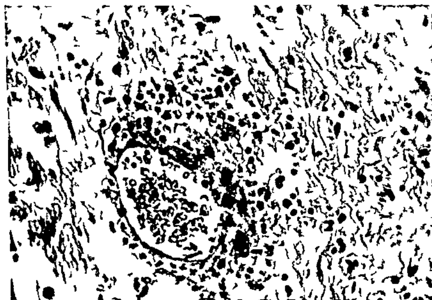


Fig 78 Rocky Mountain spotted fever skin lesion thirteenth day [illegible] Swelling of endothelial cell perivascular exudate From Dr R D Lillie Pathology of Rocky Mountain Spotted Fever U S Public Health Service)

No specific treatment has become recognized except hyperimmune rabbit serum which is useful only during the first days. Early removal of the tick may prevent infection. A specific vaccine from egg yolk culture is of prophylactic value.[573]

Fièvre Boutonneuse, Marseilles Fever, or Fièvre Exanthématique Escarro Nodulaire

Fièvre boutonneuse, Marseilles fever, or fièvre exanthématique escarro nodulaire is a rickettsiosis of the Mediterranean areas. It is transmitted by a tick which feeds on dogs carrying the causative organism, Rickettsia conori. The course resembles mild typhus, the mortality rate being less than 3 per cent. The rash is more papular than in typhus[596] and later often purpuric. Cases without eruption occur.[597] The rash starts on the trunk, legs, and arms and involves the face last. The palms and soles are commonly involved, the abdomen staying relatively free. At the onset the tick bite is frequently visible as a lentil sized shallow ulcer with a black necrotic center. This lesion is called tache noire.[597] It is of diagnostic importance but not always recognizable.

Tsutsugamushi Disease, Japanese River Fever, or Scrub Typhus

Tsutsugamushi disease, Japanese river fever or scrub typhus is a rickettsial disease of the west Pacific area. It is endemic in flooded areas and along rivers. The cause, Rickettsia orientalis, is transmitted by a mite which infests rodents, especially rats and a field vole.[598] According to Dyer[573] the disease takes a *typical typhus course of about seventeen days duration. The infecting bite* causes a necrotic or scab covered ulcer in about 75 per cent of the cases. The primary lesion is 2 to 10 mm. in diameter with an indurated red areola and is accompanied by a smooth, tender, nonsuppurative lymphadenitis which only rarely extends beyond the portal area.[599] The initial eschar is of diagnostic value. The rash, which appears on the fourth day, is noticeable only in about one half of the cases[600] and is often preceded by a dusky flush on the face and neck.[599] It resembles that of spotted fever although Dyer[573] emphasizes the lack of hemorrhagic tendency. Characteristic eye ground changes and generalized peripheral lymphadenopathy are almost constant findings. The disease was known to have a fatality rate of 15 per cent, but in a recent series of sixty-four cases only 1.5 per cent of the patients died.[600] No specific therapy and no vaccine have been developed.

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[596] Boinet, E. J., and Dunan: Recherches nouvelles sur la fièvre exanthématique du littoral méditerranéen. Bull. Acad. de méd., Paris 100: 948-960, 1938.

[597] Raybaud, A.: Tache noire et fièvre boutonneuse. Bull. Soc. path. exot. 30: 667, 1937.

[598] Blake, F. G., Maxcy, K. F., Sadusk, J. F., Jr., Kohls, G. M., and Bell, E. J.: Tsutsugamushi Disease (Scrub Typhus, Mite-Borne Typhus) in New Guinea: Epidemiology, Clinical Observations and Etiology. Am. J. Hyg. 41: 243, 1945.

[599] Ahlm, C. E., and Lipshutz, J.: Tsutsugamushi Fever in the Southwest Pacific Theater. J. A. M. A. 124: 1095-1100, 1944.

[600] Machella, T. E., and Forrester, J. S.: Tsutsugamushi Disease. Am. J. M. Sc. 210: 38, 1945.

Trench Fever or Wolhynia Fever

Trench fever or Wolhynia fever a benign recurrent fever common among soldiers of World War I is caused by a rickettsia found in the epithelial cells of the stomach of the body louse [601] The observations on the frequency of macular micropapular scarlatiniform or petechial rashes and of erythematous enanthems vary widely [573, 601, 60]

Carrion's Disease (Bartonellosis) Verruga Peruviana

In 1885 Daniel Carrión a Peruvian medical student inoculated himself with blood and tissue from a lesion of verruga peruviana an eruptive disease occurring in certain South American valleys mainly in Peru He died five weeks later of *Oroya* fever a clinically very different syndrome This experiment strongly suggested the etiological identity of the two diseases which after much controversy has become generally accepted The cause of both forms which may occur independently simultaneously or successively [603] is Bartonella bacilliformis a minute rod shaped parasite of the red blood cells Culture (Battistini after Fox[604]) and animal inoculation[605] have been successful [604, 606] The infection is transmitted by the sandfly *Phlebotomus verrucarum* the habitat of which corresponds to the few areas of endemic Carrión's disease Fifteen to forty days after the infection the patient comes down with irregular fever malaise and anemia If the disease takes the course of Oroya fever which has a mortality of 40 per cent the onset is sudden and the fever is at first continuous later remittant The main feature is an acute severe anemia with a blood picture which resembles that of pernicious anemia The red count may fall as low as 500 000 In addition there is a leukocytosis of about 20 000 Fox[604] remarks that there is probably no condition except hemorrhage which can cause severe anemia so quickly The erythrocytes contain bartonellas in great numbers Skin lesions are scanty They are more numerous in the benign form called *verruga peruviana* which has the same incubation period but in which the fever and anemia are less severe

The Spanish word verruga is used for all types of cutaneous excrescences and it should not be taken as a synonym for the dermatological term verruca The characteristic lesions of the disease are nodules or tuberous masses which vary from pinhead to apple size and from a few usually large lesions to innumerable *small efflorescences One therefore* speaks of miliary and nodular forms although there are many transitions The rash comes on in crops and is itchy especially when it heals The duration of the cutaneous form is variable on

[601] Jungmann P Das wolhynische Fieber Berlin 1919 Julius Springer
[602] Schittenhelm A Wolhynisches Fieber oder Fünftagefieber Handb d inn Medizin Vol I Berlin 1925 Julius Springer
[603] Mc B Present Status of Human Bartonellosis Bol Of san panam 22 301-309 1943 Abstr Trop Dis Bull 40 904 1943
[604] Fox H Verruga Peruana—Personal Experiences in Peru J A M A 104 98 991 1935
[605] Jadassohn J and Seiffert Über einen Fall von Verruga peruviana Übertragung auf Aff Ztschr f Hyg u Infektionskrankh 66 4 1910
[606] Da Rocha Lima H Verruga peruviana oder Carrionsche Krankheit (Oroyafieber) Handb d H u Gk 11 1 215 1932

the average from four to six months (Odriozola[607]) The miliary verrugas appear quite symmetrically on the extensor surfaces of the limbs on the ulnar aspects of the hands and forearms [607] and on the face The body the palms and soles and the genitalia usually remain free [604] The individual lesion starts as a flat red hemorrhagic papule There are subcutaneous and cutaneous lesions the depth explaining the variations in color The nodule grows so that at first a sessile and later a pedunculated bluish red conical or hemispherical tumor on a base of ringlike pigmented folds results The lesions are firm at first but soften later Small lesions look like senile hemangiomas [604] The verrugas bleed easily If the verruga is at its height the surface is glossy a little moist and the color cherry red much like a fresh hemangioma or granuloma telangiectaticum The verruga has a marked spontaneous healing tendency It may shrink or drop by atrophy of the base Bleeding is common and secondary infection occurs Lesions in the mouth the nose and the conjunctivae have often been observed They have been found in the entire length of the gastrointestinal tract and on the serous membranes These lesions may cause serious hemorrhages [607]

Very large intracutaneous and subcutaneous sarcoid infiltrations of irregular shape may develop probably by coalescence of nodules Large ulcerated granulomas are called mulas because the Peruvians believe that these big forms stem from infected mules Infantile cases are usually mild

The histological picture shows a sharply bordered vascular granuloma which consists mainly of endothelial cells (verruga cells) and inflammatory infiltration There are many variations some suggesting sarcoma angioma or myxoma [604]

Da Rocha Lima[606] and other authors found in the protoplasm of the verruga cells inclusion bodies which were considered to be an adaptation of the bartonellas to intracellular life

The diagnosis rests on the unique dermatological aspect the history of a stay in a verruga area the fever and blood picture agglutination [605] and finally on the biopsy Leprosy and yaws must be ruled out

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[607] Odriozola F La maladie de Carrion ou la Verruga Peruvienne Paris 1898 Carré & Naud
[608] How C Carrion's Disease Arch Int Med 72 147 1943

Chapter VIII

SYSTEMIC INFECTIONS

Mycoses

Fungus infections are among the most common skin diseases but systemic mycotic infections are rare if one does not count the trichophytids

Coccidioidomycosis

The name coccidioidomycosis is preferable to coccidioidosis a term which may easily be confused with the protozoonosis coccidiosis The disease is endemic in dry dusty areas of some western states [609] especially the San Joaquin Valley in Southern California [610] [611] where from December, 1937 to May 1939 432 acute infections of San Joaquin Fever were registered There is a peak of incidence in the fall It is to the great merit of Dickson[610] to have shown that the acute respiratory infection known as San Joaquin Valley fever is the primary stage of coccidioidomycosis The danger of such an endemic focus is illustrated by the fact that during recent military maneuvers in one of the endemic areas probably far more than the known seventy five cases occurred among several thousand soldiers [611]

The cause is the fungus *Coccidioides immitis* which has a saprophytic hyphae phase and parasitic spherules or cysts which are double contoured refractile bodies which break up into radially arranged segments (endospores) In the infected person or animal these spores develop new spherules The infection is mainly air borne and but rarely occurs through the skin The acute disease does not seem to be contagious from man to man as shown by the failure to infect even a bedfellow

The air borne parasite causes a *primary lung infection* which probably often remains asymptomatic but may manifest itself by severe chest pain, irritating cough severe headache prostration and fever The whole syndrome resembles influenza or pneumonia [613] In rare instances a primary lesion is found in the skin [614] A transient macular initial rash has been observed in some patients

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[609] Smith C E Epidemiology of Coccidioidomycosis With Erythema Nodosum Am J Pub Health 30 600-611 1940

[610] Dickson E C Primary Coccidioidomycosis the Initial Acute Infection Which Results in Coccidioidal Granuloma Am Rev Tuberc 38 711-7 1938

[611] Smith C E Coccidioidomycosis M Clin North America 27 790-807 1943

[612] Goldstein D M and Louis S Primary Pulmonary Coccidioidomycosis War Med 4 299-317 1943

Winn W A and Johnson G H Primary Coccidioidomycosis—Roentgenographic Study of Forty Cases Ann Int Med 17 407-427 1942

[614] Kessel J F Coccidioidomycosis Am J Trop Med 21 447-453 1941

Fig. 59.—Erythema nodosum-like rash in systemic coccidioidomycosis (San Joaquin fever). (Courtesy Dr. C. E. Smith.)



Fig. 60.—Coccidioidomycosis: scrophuloderma-like lesion about the neck. (Courtesy Dr. H. P. Jacobson.)

Within the first three weeks of the acute respiratory phase erythema nodosum of typical distribution along the shins about the knees and on the lateral surfaces of the thighs or erythema multiforme on the arms and occasionally on the face may break out Goldstein and Louie[614] found an incidence of 25 per cent among infected soldiers all of whom probably were newcomers in the area but other percentages are much lower about 4 per cent[615] Occasionally a morbilliform eruption has been noticed[611 616 617 618] Severe arthritic pains sometimes with swelling of the joints[619] have given rise to the term desert rheumatism Conjunctivitis is sometimes a feature of this stage Eosinophilia is a frequent finding Smith[611] *stresses the appearance of erythema nodosum at the time the* coccidioidin test becomes positive

The prognosis of the primary acute febrile phase is good the mortality being less than 1 per cent After recovering from an attack of San Joaquin fever the patient usually remains in good health without further attacks The coccidioidin test remains positive for a long time

The diagnosis of primary coccidioidomycosis is hardly made from the *clinical picture alone although tuberculosis like X ray changes in the lungs*[613] with negative bacillary and allergic findings may suggest it The history of having lived in an endemic area the finding of spherules in the sputum and a positive coccidioidin skin test secure the diagnosis The cutaneous reaction becomes positive two to seventeen days after the onset of symptoms In about 1 out of 1000 cases a progressive secondary granulomatosis develops which is fatal in more than 50 per cent and may predominantly involve the respiratory tract the bones the central nervous system and least often the skin Coexistence of lung foci in cases which clinically seemed to be restricted to the skin has been demonstrated at post mortem[620] Several clinical varieties of a severe dermatosis have been described Jacobson[621] classifies the lesions into those of cutaneous subcutaneous and lymphadenitic origin The skin nodules which in their further development may invade the subcutis are mainly found on the face about the neck and on the distal parts of the extremities The nodules are painless deep seated and pink to dusky red They occur in various sizes and shapes and finally ulcerate and exude a grayish yellow pus containing *Coccidioides immitis* From these dermic lesions fungating papillomatous granulomas may arise creating a picture resembling mycosis fungoides Widespread cutaneous lesions may heal with atrophic scars Chronic sarcoid and lupus vulgaris like *pictures have been observed*[622]

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[615] Willett F M and Weiss A Coccidioidomycosis in Southern California Report of New Endemic Area With Review of 100 Cases Ann Int Med 23 349 1945

[616] Goldstein D M and McDonald J B Primary Pulmonary Coccidioidomycosis 7 Ca J A M A 124 557 561 1944

[617] Faber H K Smith C E and Dickson E C Acute Coccidioidomycosis With Erythema Nodosum in Children (San Joaquin Fever) J Pediat 15 163 171 1939

[618] Dickson E G Coccidioides Infection Ann Int Med 59 10 9 1937

[619] Rosenberg E F Dockerty M B and Meyerding H W Coccidioidal Arthritis Treated by Sulfanilamide and Roentgenotherapy Arch Int Med 69 238 50 1942

[620] Epstein E Prognostic Significance of Cutaneous Lesions in Coccidioidal Granuloma Arch Dermat & Syph 38 75 755 1938

[621] Jacobson H P Immunotherapy for Coccidioidal Granuloma Arch Dermat & Syph 40 521 540 1939

[622] Zeisler E I Chronic Coccidioidal Dermatitis Arch Dermat & Syph 25 5 71 1932

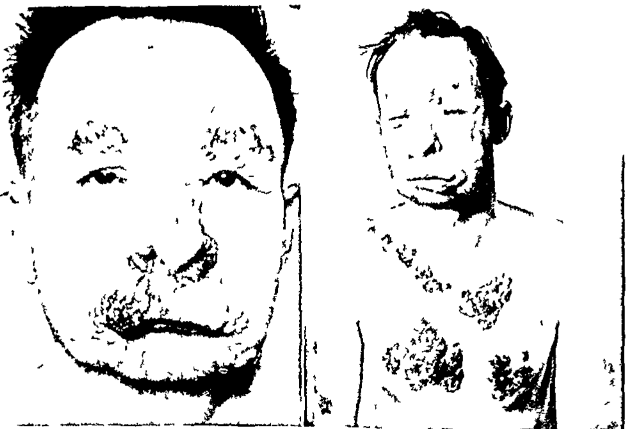


Fig 81

Fig 82

Fig 81 —Cocci lioidal dermatitis Verrucous papules (From Z isler E P Arch Dermat 193?)
Fig 8 —Chronic coccidioidal dermatitis later stages r semi ling blastomyco is (From Z i ler F P Arch Dermat 1932)



Fig 83

Fig 84

Fig 83 —Chro ic cocci lioidal dermatitis Cru ted acti lesions and annular pigm nted scars (From Zei ler F I Arch D rmat 1932)

Fig 84 —Cocci lioidom osis Granuloma with giant c ll containi g a sporulating cyst with car sule ruptured at one end (From Z isler F I Arch Dermat 1932)

The appearance of acute miliary pedunculated or sessile dermic granulomas usually on the face is of ominous significance[60] Their appearance is often preceded by symptoms of pulmonary or meningeal involvement Such patients usually succumb to the coccidioidal infection in from six to twelve weeks after the appearance of the eruption In some of these cases the fungus could be grown from the blood

The course of the subcutaneous and lymphadenitic lesions is more chronic and relatively more benign The subcutaneous granulomas are frequently the first cutaneous manifestations[63] They start as soft frequently tender masses anywhere on the body and may form large flaccid tumors cold abscesses and sinuses If the flaccid tumor or abscess is surrounded by an extensive inflammatory infiltrate a hard gummalike lesion results Finally just as in tuberculosis to which many clinical parallels exist specifically involved superficial lymphatic nodes may especially in the submaxillary region create scrophuloderma like lesions with abscesses sinuses and scars

The histopathology of the coccidioidal lesions is that of an inflammatory granuloma with marked tuberculoid tendencies There is edema and a diffuse cellular infiltrate predominantly composed of lymphocytes epitheloid and giant cells of the Langhans type These giant cells harbour the coccidioidal spheres which have been demonstrated in the process of rupturing and releasing the spores[61,6]

The treatment is still unsatisfactory Jacobson[61] who has had wide experience with coccidioidomycosis reviewed in 1939 the many methods of treatment Intravenous injections of a 1 per cent solution of antimony and potassium tartrate[64] intramuscular injection of colloidal copper oral administration of potassium iodide arsenic or combinations of these agents and roentgen therapy have not given convincing results Jacobson[61] now feels that immunizing therapy is superior to the chemotherapy known so far and has had 20 per cent good results (personal communication) The patients are in intervals of one to two weeks given intravenous injections of vaccine starting with 0 05 c c and increasing by 0 05 c c each time A course consists of twelve injections Between the courses is a rest period of six to eight weeks[65]

TORULOSIS

Only a few cases of systemic infection with the yeastlike fungus *Torula histolytica (Debaryomyces neoformans)* are known Tuberculosis resembling granulomas in the brain the lungs the gastrointestinal tract and other organs is the outstanding feature of the disease The comprehensive monograph of

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[63] Evans N and Ball H A Coccidioidal Granuloma—50 Cases J A M A 93 1881 19[illegible]

[64] Cary W H and Jacobson F M Granuloma Coccidioides Arch Dermat & Syph 16 308 19[illegible]

[65] Stewart R A and Kimura F Skin Test for Coccidioidal Infection J Infect Dis 66 212 217 1940

Stoddard and Cutler[626] emphasized the *lack of skin manifestations* Since then a few cases with dermadromes have been reported [627–630]

Acneiform pustules granulomatous ulcers and deep seated abscesses nodules or plaques[630] varying from almond to hand size without ulcerative tendency have been observed The histopathologic characteristics of cutaneous torulosis include tuberculoid granulomas with caseation and enormous numbers of giant cells *containing the double contoured oblong or spheroid refractile organisms* There exists a close similarity between torulosis and coccidioidomycosis [627]

Blastomycosis

H Montgomery[631] complains about the loose use of the term blastomycosis He suggests that the word should be used only for the disease described by Gilchrist[632] *in 1896* and not for all *infections caused by yeastlike organisms*

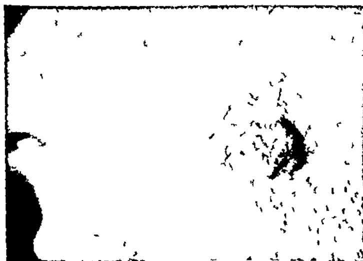


Fig 85 —Blastomycosis *Primary lesion of cheek resembling tuberculosis verrucosa*

The American blastomycosis is caused by the yeastlike fungus *Zymonema dermatitidis* which can be demonstrated in the pus or in the tissues as a refractile double contoured budding round organism often appearing in unequal pairs

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[626] Stoddard J L and Cutler F C Torula Infection in Man Monograph 6 New York 1916 Rockefeller Institute for Medical Research

[627] Urbach F and Zach F Generalisierte Torulose (Europäische Blastomykose) Arch f Dermat u Syph 162 401-4 1 1930

[628] Rappaport B Z and Kaplan B Generalized Torula Mycosis Arch Path 1 720 19 6

[629] Wellman F D Cutaneous Torulosis South M J 26 851 863 1933

[630] Wile U J Cutaneous Torulosis Arch Dermat & Syph 31 58-66 1935

[631] Montgomery H Systemic Blastomycosis M Clin North America 14 651-662 1930

[632] Gilchrist T C Blastomycetic Dermatitis Johns Hopkins Hosp Rep 1 269 1896

PLATE I

1 Acute septicemia Bullous rash with hemorrhagic component Fatal outcome

2 Acute septicemia Purpuric bullous rash

3 Lupus vulgaris planus Note brownish spots under glass pressure

4 Tubercular ulcer of the tongue in pulmonary tuberculosis (Case of Dr Jay Goodman)

5 Systemic blastomycosis Progressive skin lesion

6 Systemic blastomycosis Progressive and stable lesions













PLATE I



Fig 86 —Blastomycosis Leg lesion Not bulging edge with small ab ce In the pus of th e absce se one i likely to find the yea t



Fig 87 —Blastomyco i Small kin l ion in y temi infection

The organism grows well on the usual fungus media where it develops mycelia which are not found in the lesions

Blastomycosis may occur as a primary skin infection and in the majority of the cases it remains a dermatosis A fraction of the skin cases may become systemic and involve other organs setting up internal foci which may metastasize and thus secondarily involve the skin[631] The widely scattered subcutaneous rather indolent nodules may develop slowly into cold abscesses which may reach large size The even and symmetric distribution of nodules and abscesses and *their frequent involvement of the covered parts* in contrast to the ectogenous lesions which favor the face arms and hands indicate their hematogenous pathogenesis The abscesses may form ulcers and sinuses from which typical blastomycotic skin lesions may arise



Fig 88 — Blastomycosis Gumma like hematogenous lesion

The primary skin lesion of blastomycosis is a papulopustule which slowly grows peripherally Within a few months it forms[633] a coin shaped thick firm elevated patch the surface of which is papillary or verrucous and often fissured *or lobulated The center becomes depressed as soon as the lesion has reached* the size of about a half dollar The most characteristic feature is the steeply raised succulent red border in which many pin point to pinhead sized abscesses are contained By means of pressure and a magnifying glass they can easily be made visible The small quantity of pus which can be expressed from the tiny abscesses is the best material for microscopic study and culture The lesions may by growth and coalescence attain large size and even cover entire regions The center of such large lesions is often scarred but there are active *foci scattered throughout the scar tissue* in varying density The active foci in old lesions are often crusty oozing with serum and pus and apt to bleed on the slightest touch The destructive power of such large blastomycotic granulomas

[633] Ormsby O S and Montgomery H Diseases of the Skin Philadelphia 1943 Lea & Febiger

is great Prominent soft parts for example the scrotum [633] the alae nasi and the lids may suffer great damage The polycyclic border of old lesions remains more or less papillary often cordlike The scarring does not always keep pace with the extension of the lesions so that large areas may remain thickly covered with red beds of vegetating masses In other cases the peripherally progressing border leaves in its wake a smooth red ulcerative area almost devoid of any healing tendency



Fig 89 Unusually severe systemic blastomycosis This type of blastomycotic lesion resembles tuberculosis cutis verrucosa This case healed after three months of treatment with iodin and x ray (From Bush J D Arch Dermat 1941)

In 50 per cent of the systemic cases the first symptoms are referable to the respiratory tract The picture may resemble that of a cold or of an attack of influenza In 4 per cent the primary lesion followed an injury in 19 per cent a skin lesion was noted first and in 23 per cent the earliest lesion was a subcutaneous nodule or abscess often on unexposed parts [634] Besides a great variety

[634] Martin D S and Smith D T Blastomycosis Review of Literature Am Rev Tuberc 39 275-304 488 515 1939

of occasional organic involvements the bones mostly the vetebrae and joints become infected in about 50 per cent of the systemic cases

The histopathology reveals a granuloma with varying mixtures of leukocytes lymphocytes plasma cells and Langhans type giant cells which often contain some fungus elements Tubercle formation is not marked

Enormous acanthosis and miliary abscesses throughout the hypertrophic rete as well as the corium are characteristic features

The reservoir of the infecting fungus is probably on certain plants Infection from man to man occurs only under extraordinary circumstances The only such case known is that of a physician who injured himself at the necropsy of a case of systemic blastomycosis (Evans after Martin and Smith[634])

The age incidence has its peak between 20 and 40 years Men are nine times as often infected as are women The disease is far more common among the poorer classes [634]

The prognosis of the systemic cases is almost invariably fatal The localized primary skin infection may take a chronic course but it will finally heal unless it becomes systemic which is unusual

Clinical diagnosis from the skin lesions is often possible Other myco es tuberculosis verrucosa syphilis and fungating granulomas must be ruled out The detection of the organism in the pus of small abscesses microscopically or by culture will usually confirm the clinical diagnosis For the microscopic examination the material is covered with a drop of 40 per cent KOH and examined in minimal light after at least ten minutes A vaccine from heat killed fungi[634] is used in the diagnosis and treatment

Treatment —Excision of small lesions may occasionally arrest the disease Irritating substances such as caustics often make the condition worse Potassium iodide in huge doses up to 25 Gm daily [633 635] has often healed and often failed but it is nevertheless still the method of choice Combination with X ray therapy and vaccine may be judiciously used in combination with potassium iodide which loses its effect after prolonged administration Martin and Smith caution against the indiscriminate use of potassium iodide in hypersensitive cases These cases should be desensitized by a series of vaccine injections

[635] Bu h J D Blastomycosis Arch De mat & Syph 43 485 490 1941

CHAPTER IX

HELMINTHIC DISEASES

Trichinosis

It is now well established that trichinosis is a common human infection in the United States A great number of post mortem diaphragm examinations conducted in various parts of the country[636-640] have shown that 12 to 18 per cent of the cadavers harbor trichinae The infection stems largely from inadequately cooked pork rarely from the meat of bears wild boars and some other large animals A main source of infection of the swine is the practice of feeding them uncooked scraps of pork while trichinous rats play a minor role[637] On ingestion of trichinous meat the dormant and encysted worms are freed by the gastric juice They propagate in the small intestine after one week The young worms which are smaller than a red blood cell are carried by the circulation to the muscles Here they grow and encapsulate and may live for as many as thirty years

The clinical picture of human trichinosis depends on such factors as massive infection or small size of the patient tissues invaded general resistance and concomitant pathological conditions[637] Many cases pass symptomless or undiagnosed The clinical course can be divided roughly into three stages (Davaine after Beeson[641]) but it must be emphasized that this clearly defined sequence is seldom observed in practice There is an initial gastrointestinal phase starting sometimes hours after the ingestion of trichinous meat At the end of the first week it is followed by a stage of dissemination marked by prostration facial edema fever sweating and pain in the muscles of respiration mastication and the eye After six weeks the disease passes gradually into the stage of encystment of the worms in the muscles while the severe symptoms ease up and the fever subsides Edema muscular pains and anemia may persist for a long time The average mortality which was very high in some German epidemics of the nineteenth century is probably less than 5 per cent of the clinical cases in the United States[64] Most deaths occur from the fourth to sixth week and are due to myocarditis or bronchopneumonia[639] There are indications that existing infection protects against reinfection[643]

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[636] Hall M C and Collins B J Studies on Trichinosis Pub Health Rep 52 468-490 1937

[637] Hall M C Studies on Trichinosis Pub Health Rep 52 539-551 1937 53 1472 1486 1938

[638] Kerr K B Jacobs L and Cuvillier E Trichinosis Post mortem Examination of 3 000 Diaphragms From Washington D C and Five Eastern Seaboard Cities Pub Health Rep 56 836 855 1941

[639] Gould S E Trichinosis Springfield Ill 1945 Charles C Thomas Publisher

Gould S E Method fo Control of Trichinosis in th U S A J A M A 129 1251 1254 1946

Beeson P B Trichinosis—Clinical Manifestations Lancet 1941 - 6 -69

[642] Blumer G Trichinosis Connecticut M J 4 314-317 1940

[643] Wyrens R G Tillisch J H and Magath T B Trichinosis J A M A 117 425-437 1941

The blood changes are characteristic There may be severe anemia and leukocytosis *Eosinophilia* is an almost invariable sign in the second stage It may range from a few to 73 per cent[644] and is considered the most reliable diagnostic sign[645] However eosinophilia may be missed or disappear in severe cases[644]

A cutaneous *immediate urticarial reaction* with an allergen from digested trichinous meat has been developed by Bachman[646] Besides the immediate response which appears within thirty minutes a *delayed* reaction may occur after two days This test is supposed to become positive in the third week of illness[159 647 648] The reaction is about as reliable as the precipitin reaction which becomes positive in the fourth week[649] or as the complement fixation test[650] Considering the frequency of trichinella infection a positive skin reaction is only *valuable if supported by other evidence of recent infection or if it has turned* positive while the disease has been observed[159] The test* may be negative in very severe cases[159 651 65] In all tests group reactions against other common worm infections must be borne in mind[653] For example Fulleborn[654] mentions a case of a patient infected with echinococcus who gave a positive reaction to echinococcus antigen as well as to antigen from *Cysticercus tenuicollis* trichinella and strongyloides There is also a common antigen in ascaris and trichinella[159] and pinworm and trichinella[548] Muscle biopsy (gastrocnemius) is rarely necessary The muscle specimen should be pressed between two glass slides and examined at low power as is done in the testing of meat Trichinae can occasionally be centrifuged from the stools the bile the arterial blood[655] or the cerebrospinal fluid[651]

Dermadromes —The scarcity of cutaneous lesions is in agreement with the rarity of the presence of trichinae in the skin of experimentally infected mice[656]

Edema of the eyelids is the most common and in fact the only dermadrome which is seen in the majority of the cases It is an early important sign of mus

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* The allergen can be obtained from the National Institute of Health in Bethesda Md which also does the precipitin test on serum sent in for this purpose

[6] Murphy F D James H D and Rastetter J W Trichinosis 93 Cases Am J M Sc **199** 328-338 1940

[645] McNaught J B Laboratory Procedures for the Diagnosis of Trichinosis Am J Clin Path Tech Sect **8** 87 93 1944

[646] Bachman G W An Intradermal Reaction in Experimental Trichiniasis J Prev Med **2** 513 5 3 19 8

[647] McNaught J B *Diagnosis of Trichinosis Am J Trop Med* **19** *181 192 1939*

[648] Hall A A Trichiniasis Use of the Bachman Intradermal Skin Test Ann Int Med **10** 1544 1550 1937

[4] Kaufman R E Trichiniasis Clinical Considerations Ann Int Med **13** 1431 1460 1940

[650] Gaase A Trichinosis Serodiagnosis With Complement Fixation München med Wchnschr **88** 473-474 1941

[651] McNaught J B Medical and Public Health Aspects of Trichinosis Texas State J Med **38** 252 55 194[illegible]

[652] McNaught J B Beard R R and Myers J D Diagnosis of Trichinosis by Skin and Precipitin Tests Am J Clin Path **11** 195-201 1941

[653] Jadassohn W Die Immunbiologie der Haut Handb d H u Gk **2** 418 193[illegible]

[654] Fülleborn F Diagnostische Cutanreaktion bei Helminthenkrankheiten Klin Wchnschr **7** 8 0 19[illegible]

[655] Dammin C J Trichinosis—Report of a Case With Demonstration of Larva in Arterial Blood New England J Med **224** 3 7 360 1941

[656] Mauss E A and Otto G F Occurrence of Trichinella Spiralis Larvae in Tissues Other Than Skeletal Muscles J Lab & Clin Med **27** 1384 1387 19[illegible]

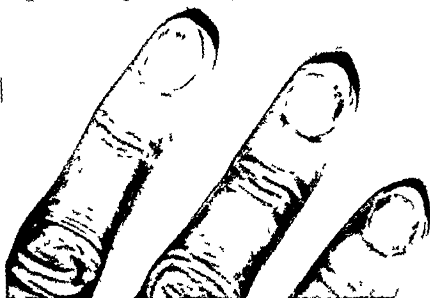


Fig. 90.—Splinter hemorrhages in trichinosis. (Courtesy McNaught, J. B.: Am. J. Trop. Med., 1939.)

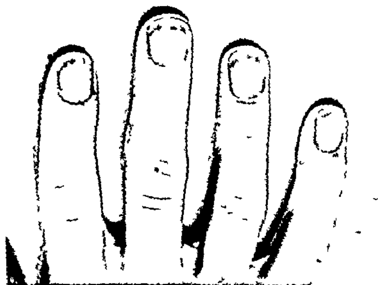


Fig. 91.—Trichinosis. Splinter hemorrhages arranged in cross lines indicating simultaneous genesis. (Courtesy Dr. Beeson.)

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[644] Murphy F D James H D and Bastett J W *Trichinosis 23 Cases Am J M Sc* **199** 328 338 1940

[645] McNaught J B *Laboratory Procedures for the Diagnosis of Trichinosis Am J Clin Path* Tech Sect **8** 87 93 1944

[646] Bachman G W An Intradermal *Reaction in Experimental Trichinia is J Exper* Med **2** 513 5 3 1928

[647] McNaught J B *Diagnosis of Trichinosis Am J Trop Med* **19** *181 197 1939*

[648] Hall A A Trichinosis Ua of the Bachman Intradermal Skin Test Ann Int Med **10** 1514 1550 1937

[649] Kaufman R F Trichinosis Clinical Considerations Ann Int Med **13** 1431 1460 1940

[650] Gaase A Trichinosis Serodiagnosis With Complement Fixation München *med* *Wchnschr* **88** 473-474 1941

[651] McNaught J B Medical and Public Health Aspect of Trichinosis Texas State J Med **39** 252 255 1947

[652] McNaught J B Beard R R and Myers J D Diagnosis of Trichinosis by Skin and *Pre*cipitin Test Am J Clin Path **11** 195- 01 1941

[653] Jadassohn W Di Immunbiologie der Haut Handb d H u Ck **2** 418 197

[654] Fülleborn F Diagnostisch Cutanreaktion bei Helminthenkrankheiten Klin Wchnschr **7** 8 0 19 8

[655] Dammin C J Trichinosis Report of a Ca With Demonstration of Larva in Arterial Blood New England J Med **224** 35 360 1941

[656] Maus E A and Otto G F Occurrence of Trichinella Spiralis Larva in Tissues Other Than Skeletal Muscles J Lab & Clin Med **27** 1345 1347 194

Ancylostomiasis (Hookworm Disease)

Ancylostomiasis (Hookworm Disease) The hookworms[664] for medical purposes the genera ancylostoma and necator are duodenal human parasites whose larvae leave the bowel with the feces in great numbers These larvae are about 0 5 mm long They enter the body through the unbroken skin especially the thin skin of the instep area and are carried by the lymph and blood to the lungs from where they follow the bronchotracheal tree into the larynx pharynx and finally the gastrointestinal canal (Looss after H Bruns[665]) to their living and breeding place the duodenum The hookworms are found chiefly in warmer climates They have caused epidemics in warm countries among barefooted workers on rice tea mulberry and similar plantations and in colder climates among miners working in the warm and humid shafts

The disease is common in the southern section of the United States and especially in Puerto Rico The infection causes a severe often fatal progressive anemia and involvement of many organs

Dermadromes —When the larvae penetrate the skin of the feet they cause itching vesicular dermatitis and possibly secondary infection However a controversial point is to what extent hookworm causes the ground itch of the south or mazamorra of Puerto Rico and Central America a common eczematous condition of the feet Fulleborn[664] denies that the majority of the ground itch cases have anything to do with ancylostomiasis It is claimed that *Necator americanus* is more likely to cause ground itch than *Ancylostoma duodenale*[548]

If the hookworm infection has become fully developed *pruritus* marked *dryness* of the skin and hair reduced perspiration on exertion and heat and *burning of the palms* are reported to be troublesome symptoms (Ashford and King after Fulleborn[664] The features are reported to become blurred and slightly puffy shift of pigment takes place[666] and persistent acne may occur A butterfly shaped pigmentation over the bridge of the nose has at times been thought to be diagnostic of schistosomiasis but this is not true since such pigmentations occur also in other infections (bilharziosis) and probably also in various nonhelminthic conditions The diagnostic value of minute black or brown spots on the side of the tongue or on the lips in patients with hookworm is doubtful[667 668]

Creeping eruption caused by the larvae of *ancylostoma braziliense* and other nematodes is not always restricted to the skin[669 670] It may like other worm

[664] Fülleborn F Haut und Helminthen Handb d H u Gk 12 1 708 800 193_

[665] Bruns H Di Ankylostomiasis in d r gemässigten Zone Handb d path Mikroorg 6 2 907 918 19 9

[666] Ba rmann G Di Ankylostomiasi d r Tropen und Subtropen Handb d path Mikroorg 6 2 949 994 19 9

[667] Sutton R L and Sutton R L Jr Dis ases of the Skin St Louis 1939 Th C V Mosby Co

[668] Jeghers H Pigm ntation of th Skin New England J Med 231 88 100 122 136 181 189 1944

[669] Millspaugh J A an l Sompayrac L M Hookworm Infectio Creeping Eruption Infestati n With Ancylostoma Brazili U S Nav M Bull 40 393-396 194_

[670] Kirby Smith J L Do e W E and White G F Creeping Eruption Arch Dermat & Syph 13 137 175 1926

infestations and some bacterial infections be accompanied by transient and migratory pulmonary infiltrations with few or no symptoms This is known as *Loeffler s syndrome*[671]

Ascariasis

Infestation with large roundworms has been held responsible for a number of dermatoses It is certain that ascarides contain a highly sensitizing allergen which may explain cases of urticaria angioneurotic edema pruritus nasi epistaxis and eczema The same precaution as is used in the evaluation of allergic tests *in other worm infections (see under trichinosis) must be used in the skin* tests for ascarides[646 664 67 673] The possibility of anaphylactic shock with asthma and urticaria in repeated intracutaneous tests with ascaris antigens is emphasized by several authors[673] Another difficulty is that at least in some areas for example the southeastern parts of the Appalachian range[648] the incidence of a sensitization to ascaris is so widespread among the population that the test loses its diagnostic value[674] The pathogenesis of some skin lesions for instance pruritus ani eczema of the hands itching of the nose and bullous or acneiform eruptions[675] may be explained by local reactions to the worm allergen in ova carried and inoculated by the hands Several observers have expressed the thought that the itching and scratching of the nose in worm infestation which is so common in the tropics is an important cause of the first infection with leprosy

Oxyuriasis

Similar conditions of allergy combined with the mechanically caused itching produced by the migrating worm exist in pinworm (*Enterobius* or *Oxyuris vermicularis*) infestation The worms[676] live in the lower ileum and cecum but descend to the rectum for egg laying From there they may at night reach the anus and occasionally distant skin areas Scratching and inoculating of the crushed worms or eggs may cause local allergic reactions[677] Neurodermatitis which responded to anthelmintic treatment and flared up on injection of oxyurus extract has been described[678] Biting of the nails sucking of the thumb and picking at the nose often considered suggestive of worm infection were found no more frequently in infested persons than in control groups

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[671] Wright D O and Gold E M Loeffler s Syndrome Associated With Creeping Eruption J A M A 128 1083 1083 1945

[672] Nagel R Die Cutireaktion bei Ascaris lumbricoides I tanbul Seririyati Nr 4 75 78 1037 Zbl 56 9

[673] Schönfeld W Ascaridentoxikose und Haut Arch f Dermat u Syph 175 51 70 1037

[674] Diehl F and Schwoer P Allergie der menschlichen Haut gegen Ascaris lumbricoides Arch f exper Path u Pharmakol 183 1 8 1936

[675] Schütz J Helminthenbedingte Hautkrankheiten und ihre Behandlung Dermat Wchnschr 80 807 1925

[676] Cram E B Oxyuriasis Am J Dis Child 65 46-59 1943

[677] Cieszyński F K Hautreaktionen auf Helminthesprodukte bei Kindern Monatsch f Kinderh 39 61 71 1928

[678] Schröpl E Neurodermitis durch Oxyuren Dermat Wchnschr 83 1053 1097 1926

The *diagnosis* rests on the finding of worms or their ova The latter are best collected with a few energetic strokes in a peripheral direction from the anus with a cellophane (Scotch tape) tipped swab[679] The cellophane is then examined on a slide moistened with water and covered with a cover slip A skin test with enterobius antigen may be helpful[675, 680] Brady and Wright[681] were unable to find any typical cutaneous lesions in 200 controlled cases In a series of tests Brady and Wright[681] found that gentian violet given by mouth was superior to other methods The dosage of the drug for adults was two 32 mg tablets three times a day before meals and for children 10 mg a day for each year of their apparent not actual age the total amount being divided into three doses

Filariasis

Wuchereria (*Filaria*) *bancrofti* is a nematode of the warm climates The adult worm which is as thick as a strong hair and several centimeters long lives in the human lymphatics and produces tremendous numbers of micro filariae which are about 0 3 mm long and no thicker than a red blood cell These microscopic worms live in the blood appearing in great numbers at night in the peripheral blood and retreating at day into the visceral arteries The microfilariae pass part of their development in various mosquito vectors but they are brought back into man to complete their life cycle According to Manson Bahr[5 9] Fülleborn[664] and other authorities on tropical medicine the microfilariae in spite of their number have no pathogenic properties while in a certain proportion of instances the obstruction of lympatics caused by the *adult* worm causes *lymphedema lymphatic varicosities* and *elephantiasis* The monstrous enlargements of legs mammae scrotum and other parts are well known pictures of tropical pathology The lymph stasis inflammatory reaction scarring and calcification caused by the adult worms may be permanent The lesion is likely to become infected with hemolytic streptococci causing the re peated erysipelatoid attacks which are the more immediate cause of elephant iasis[68, 683] Other authors believe that elephantiasis may develop without acute attacks[684] Grace[685] feels that there is no evidence that *Wuchereria* (*Filaria*) *bancrofti* plays any part in the production of the attacks of lymphangitis Re cent observations on military personnel in endemic areas[686] have shown that acute lymphangitis of arms or legs and acute funiculitis or epididymitis with little fever or general symptoms are the outstanding early clinical symptoms Peculiar features are a centrifugal lymphangitis which may work down from the

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[679] Hall M C Studies on O yuria is I Types of Anal Swabs a d Scrapers Am J Trop Med 17 445-453 1937

[680] Tsuchiya H a d Bauerl in T C Intradermal Test as Aid i Diagnosis of Ent robiasi J Lab & Cli Med 24 6 7-631 1939

[681] Brady F J and Wright W H Oxyu iasis 200 Cases Am J M S 198 367-37? 1939

[682] Low G C Pathology of Filariasis J Stat Med 39 594 598 1931

[683] Brug S L Filariasis a d El phantia i Ned rl tijdschr v ge eesk 76 2772 2776 193 Zbl 43 189

[684] Fl ba b L Clinical Studi s of Fila iasis Geneesk tijdschr v Nederl Indië 73 647-658 1933

[685] Grace A W Filariasi Tropi al Lymphangitis and Abscesses J A M A 123 462-466 1943

[686] Thompson K J Rifki H and Zarrow M Early Filariasis in Young S ldiers J A M A 129 1074-1080 1945



Fig 92 —Microfilaria of L loa in blood film (X1 700) Actual length 165 micro s The o ly successful preparations were made from the bloo.l taken from a Calabar swelli g on the forearm in th late afternoon Giemsa stain (From Guy W H Cohen M and Jacob F M Arch Dermat 1943)



Fig 93 —Calabar swelling From Guy W H Cohen M and Jacob F M Arch Dermat 1943)

upper arm to the waist and lymph nodes in unusual sites for example the tip of the ileum the midarm and the region of the serratus and teres muscles Centripetal lymphangitis occurs also In the chronic stages the skin manifestations are due mainly to the enormous lymphatic varicosities and enlarged lymph nodes which may cause dome shaped pseudovesicles of the skin A positive *reaction to an intradermal injection of* 1 4000 *filaria antigen* is considered diagnostic[686] Other worm infections do not respond to a dilution higher than 1 2000 *Filaria loa* an African species transmitted by a fly migrates in the connective tissue often near or in the skin or beneath the bulbar conjunctiva producing the so called *Calabar swelling* these lesions appear on the forearms or less commonly over the ankles or on the face They probably represent an allergic

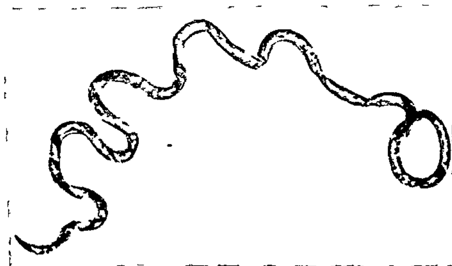


Fig 94 — F laria of L loa (×6) actual length 43 mm Adult worm r mov d from the conjunctiva of a missionary retur ed from the Cameroon Af ica Note th nuclear structure and the twist at th caudal end (From Guy W H Cohe ı M and Jacob F M Arch Dermat 1943)

reaction to the worm or its products The worm or calcified *remnants of it* have been demonstrated by roentgenogram[687] The swellings are usually rather painless but sometimes itchy They disappear after a few days or rarely after weeks[68] only to recur somewhere else[688] Scabies like itching eruptions are known as filarial prurigo or gale filarienne[689] Besides the mentioned skin tests complement fixation reactions in filariasis have been developed[690,691] Eosinophilia may reach 24 per cent[692]

[687] G eig F D W Fil riasi Ca s f Calabar Swelli g With Radiologic Obs rvations J Trop Med 43 1 -21 1940
[688] Guy W H Coh n M and Jacol F M Infection With Loa Loa Arch De mat & Syph 47 63 767 1943
[689] St fanopoulo G Filarial Prurigo o Cal Filarienne in Ca Due to Loa Loa Trop Dis Bull 40 85 1943
[690] Fairl y N H Skin Test and Compl m nt Fi ation i Filariasis Tr Roy Soc Trop Med & Hyg 25 70- 1 193
Rodhain J and Dubois A Intradermal Reacti ns in Human Filariasis T Roy Soc Trop Med & Hyg 25 3 -38 193
[692] Low G C Skin Conditions Found in Loa Loa Infections J Trop Med 37 3 9-360 1934

An eosinophilic disease with migratory edematous swellings which has lately been observed in small epidemics in Palestine probably is related to Calabar swelling[693]

Onchocerciasis

Onchocerca is a nematode which resembles filaria in many respects The life cycle which is not fully understood is partly spent in flies of the genus Simulium The adult worms and great numbers of microfilariae live in cystic tumors (onchocercomas) of the subcutis The majority of the patients with *onchocercomas present no demonstrable cutaneous manifestations However* microfilariae have been found in great numbers in apparently unaffected skin[694] as well as in the blood The onchocerca nodules are pea to almond sized and *occur most frequently over the skull which they may perforate along the costal* arches and about the joints where they may simulate juxta articular nodes There is an African type caused by *Onchocerca volvulus* and a Central American type caused by *Onchocerca caecutiens* The latter is restricted to parts of Guatemala and Mexico The American onchocerciasis is of importance because of the keratitis and iritis which accompany many cases and which may lead to blindness (onchophthalmia)[694, 695, 696] *Acute febrile erysipelatoid swellings of* the face and of the limbs characterized by hardness and a greenish hue and transitions into chronic edema occur among patients with onchocerca nodules (Robles after Fulleborn[696]) *In both types of onchocerciasis the skin may become* dry itchy infiltrated and coarsened (onchodermatitis) This pruriginous phase may look much like scabies[697] or neurodermatitis[698] The microfilariae of *Onchocerca volvulus* can be found in the altered skin *Itching seems to be* caused by allergic phenomena rather than by the active moving of the worms since heavily infected skin was found without associated pruritus[698]

Dracunculiasis or Dracontiasis (Guinea Worm)

The guinea worm (*Dracunculus medinensis* or *Fuellebornius medinensis* formerly called *Filaria medinensis*) is in its larval stage a parasite of some microscopic crustacea of the genus cyclops which infests man through drinking water or through direct entrance into the skin After one year, the adult fertilized female which is one yard long and about as thick as a thread appears under the skin sometimes preceded by fever and urticaria[699] *A dome shaped blister later an* ulcer indicates its end The lesion varies in diameter from 2 to 7 mm[700] On

[693] Leffkowitz M and Sukienik S Clinical Picture of Eosinophilic Disease With Cutaneous Manifestation Harefuah 28 12 1945

[694] Goldman L American Onchocerciasis Arch Dermat & Syph 127 39-393 1944

[695] Hoffman C C and Vargas L Nuevas communicaciones acerca de la *onchocercosis de* Chiapas Rev mex de biol 11 1 147 1931 Zbl 41 795

[696] Fulleborn F Uber Juckende Hauterscheinungen bei zwei deutschen Onchocercatragern aus Sudmexiko Nebst einer Zusammenfassung uber die auf Onchocercainfektion bezogenen Dermatosen und Versuch uber den diagnostischen Wert der Kutanreaktion mit Onchocerca Antigen Arch f Dermat u Syph 164 16-38 1931

[697] Anderson C and Lehucher J Onchocerciasis (Cutaneous) in Tunisia Arch Inst Pasteur de Tunis 29 105-112 1940

[698] Loewenthal L J A Onchocerciasis Cutaneous Changes Ann Trop Med 37 147 148 1943

douching with cool water the worm will often protrude from a small hole and expell a fluid containing thousands of embryos

The premonitory urticaria and pruritus and also asthma and diarrhea are probably caused by the same allergens in the excreta which cause the blister and ulcer The microfilariae do not have the toxic or allergenic effect of the adult worm[699] which if injured or dead sometimes causes severe reactions The therapy consists in *cautious and patient extraction of the entire adult worm* which takes about two weeks This requires a certain technique which can be found in the textbooks on tropical diseases[5 9 548 700]

Cysticercosis

Normally the adult tapeworm (usually *Taenia solium*) is a parasite of the human ileum Its eggs must get into the stomach of the swine where the hatched embryos travel to the points of encapsulation Occasionally man is the intermediate host instead of the pig Then he will harbor the encapsulated larvae most often in the brain and the eye only in 6 per cent of the cases in the subcutaneous tissues The subcutaneous or cutaneous cysticerci are cysts of from one to several centimeters in diameter They are round or oblong and are freely movable in the subcutaneous tissue The cysts are of elastic hardness and nontender numbering a few or several thousands The inflammatory reaction is insignificant If they are diagnosed they may help to explain other symptoms caused by cysticercosis of internal organs[701 705] The prognosis of cysticercosis of the skin per se is favorable The cysts usually stay without change and sometimes disappear spontaneously The huge *echinococcus* cyst is the larva of a small tapeworm of the dog The disease is very rare in the United States An intracutaneous test with liquid from the cysts (Casoni test) and a complement fixation test are reliable

The larvae of some tropical cestodes (*Sparganum proliferum*) may cause small acne like cutaneous cysts besides severe involvement[706] of almost the entire system in some of the few studied cases[664]

Bilharziasis

The adult worms of *Schistosoma hematobium* live in pairs in the portal system of man producing eggs which appear in the feces and in the urine In water

[6] Fairley N H and Liston W C Studies in the Pathology of Dracontiasis I Indian J M Research 11 915 93 19 4

[700] Fairley N H Studies in Dracontiasis VI Indian M Gaz 59 4 9–438 19 4

[1] Takamatsu H Generalized Cysticercosis Zentr lbl f allg Path u path Anat 72 … 1939

[702] Tanasescu I and Repciuc E Fl Fall von Cysticercus bovis im Unterhautgewebe des Menschen Virchow Arch f path Anat 304 … 5 8 1939

[703] Pick W Tierische Parasiten der Haut H lb d H u Ck 9 1 467 614 19 ?

[704] Brailsford J F Unrecognized Cysticercosis Lancet 1 1?7 1 8 194

[705] Hu C K Oo-K k I and Fraser C N Subcutaneous Cysticercosis Cellulosae in Man Five Cases Arch Dermat & Syph 21 777 89 1930

[706] Stiles C W and Taylor L Th Larval Cestode (Sparganum mansoni) of Man Which May Possibly Occur in Returning American Troops Bull 35 Bureau of Animal Industry U S Dept Agriculture Washington 190

they develop into larvae (cercariae) which are able to enter the human body through the skin

Bilharziasis is predominantly a urinary disease It is a public health problem of great importance in Egypt, Japan China and other countries especially where work in flooded rice fields brings about the exposure to infection with cercariae

Dermadromes —The dermadromes are of little importance in comparison with the frequent and severe bladder involvement The skin in the neighborhood of the urinary fistulae may contain huge numbers of often calcified eggs The irritation from urine pus and infestation may give rise to *papillomas* of the anal and genital region which occasionally become malignant Sinderson[707] found in 20 per cent of the schistosomiasis (hematobium) cases that he observed in Iraq a sometimes reticulated well defined butterfly shaped *hyperpigmentation* over the bridge of the nose and the cheeks He believes that it is caused by a photosensitization of the skin under the influence of the worms (see under ancylostomiasis)

The entering cercariae of schistosoma hardly cause [708] dermatitis while the cercariae of otherwise innocuous trematodes have been held responsible for many epidemics of *swimmers itch*

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[707] Sinderson H C Anomaly of Pigmentation in Schisto omiasis Tr Roy Soc Trop Med **23** 633-634 1930

[708] Lutz A and Lutz G A Bilharziosis oder Schi ostomuminf ktion n Handb d path Mikroorg **6** ? 873 906 19 9

CHAPTER X

TUBERCULOSIS

The elementary facts concerning the tubercle bacillus and the general pathology of tuberculosis are so well known that it does not seem necessary to discuss them except for some phenomena which are of special importance in the pathogenesis of the cutaneous manifestations of internal tuberculosis

If the skin of a *normal*[366, 709, 711] guinea pig is inoculated with tubercle bacilli the small wound heals primarily After a week an inflammatory reaction sets in A papule develops which during the third week forms an ulcer There is little tendency to heal and some ulceration or infiltration usually still exists when the animal dies of generalized tuberculosis During the second week lymphangitis and lymphadenitis are marked The histological picture shows at first an inflammatory reaction with many groups of tubercle bacilli During the third week tuberculoid structures start to form and the number of bacilli decreases so that only occasionally can single rods be found Tuberculin skin tests start to become positive about ten days after the infection Within four weeks the entire skin has become sensitized[710]

If the identical inoculation of tubercle bacilli is done in the skin of a guinea pig which at least four weeks *previously had been infected* with tuberculosis an acute hemorrhagic edematous and sometimes necrotic reaction starts within twenty four hours reaches its height on the second day and then subsides rapidly After about ten days a necrotic hemorrhagic crust is thrown off After three to four weeks the lesion is usually healed There is no additional lymphadenitis and no further ulceration The histological examination reveals an acute inflammation The scab which contains the bulk of the bacilli comes off the underlying erosion heals and is soon covered with normal epidermis Sometimes tuberculoid structures are formed earlier than in the primary inoculation It must be emphasized that this sequence of changes after primary and superinfection known as *Koch s fundamental phenomenon* is subject to many variations and that great skill and experience are required to produce it in complete clarity This is particularly true[366] of the experimental hematogenous i e *intracardial* infection of the guinea pig

Two weeks after the intracardial injection of tubercle bacilli normal animals develop a papulo squamous rash and die from generalized tuberculosis after four to five weeks Tuberculous guinea pigs however show during the second day a follicular rash which heals quickly after a latency of about two weeks

[709] Lewandowsky F Die Tuberkulose der Haut Berlin 1916 Julius Springer

[710] Sulzberger M B and Wise F Tuberculin New Dermatological Considerations Clin North America 14 1555 1931

[711] Martenstein H Neuere Ergebnisse auf dem Gebiete der Hauttuberkulose Die extrapulmonale Tuberkulose Vienna 19[illegible] Urban and Schwarzenberg

some papulocrustous lesions appear which heal spontaneously The microscopic picture of the hematogenous lesion in the first infected animal is that of an inflammatory reaction of nonspecific character with abundant bacilli The hematogenous lesions in superinfected animals are decidedly tubercular in structure consisting of epithelioid and typical giant cells There is periarterial necrosis but hardly any bacilli can be detected The lesions are often found in the follicular plexus [366] Similar tuberculoid lesions can be produced by the intracardial *injection of killed tubercle bacilli*

The interpretation of these experiments and many variations has been formulated by J Jadassohn[797] and his pupils especially Lewandowsky in a rule which has been amply confirmed not only in tuberculosis but also in many other infections This so called *law of J Jadassohn and Lewandowsky* states that unchecked growth of microbes causes nonspecific inflammation Where however microbes are locally and not too rapidly destroyed by the immunebiologic defensive reaction tuberculoid structures develop * This law applies to the products of microorganism

Koch s fundamental phenomenon has been found valid in the human pathology If the *skin of a person who has not had tuberculosis before is infected* with tubercle bacilli a lesion characterized by rapid ulceration lymphangitis and lymphadenitis and abscess formation develops in the course of one to two weeks [1 716] This syndrome which is best known from the cases of circumcision tuberculosis [71 18] but also from other traumatic infections [718 720] is called the primary complex of tuberculosis of the skin

The number of bacilli in the ulcer is large so that they can be found in the direct smear The tuberculin reaction is negative in the early stages but becomes positive three to eight weeks after the cutaneous infection (E Lowenstein after E H Urbach[159 7 1]) The tuberculous *primary complex* of the skin is much rarer than its pulmonary counterpart the Ghon tubercle Approximately one out of 750 cases of tuberculosis starts in the skin [[illegible]]

Tubercle bacilli—for that matter also other *microbes—spread* very rapidly from a skin infection Excision of a primary skin infection does not prevent

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* For excellent pictures on experimental tuberculosis see Sulzberger's Dermatologic Allergy (Pictures of moulages prepared under the direction of Drs O Mi h r and W Jadassohn)

[71?] Falmelius Post traumatic Primary Tuberculous Infection of the Skin Acta chir Scandinav 70 1933

Brun gaard So-Called Primary Complex of Tuberculosis of the Skin Finska läk sällsk Handl 75 1933

Franz W Der tuberkulöse Primärkomplex der Haut

Michelson H E Primary Complex of Tuberculosis of the Skin Review of the Literature Arch Dermat & Syph 32 1935

O Leary P A and Harrison M W Inoculation Tuberculosis Arch Dermat & Syph 44 371 390 1941

Wolff E Über Circumcisionstuberkulose Berl klin Wchnschr

Finkelstein L Beschneidungstuberkulose

Fisher H K The Primary Cutaneous Tuberculous Complex J A M A 108 2031 2035 1937

Schachmann C Primary Tuberculosis of Skin in Children Secondary Formation of Lupus Arch f Kinderh 118

Michelson H E Allergy and Resistance in Tuberculosis Journal Lancet

Ranke K E Ausgewählte Schriften zur Tuberkulosepathologie Berlin 1928 Julius Springer

Ghon A The Primary Complex of Human Tuberculosis Am Rev Tuberc 7 314 1923

Sallick M A Primary Cutaneous Complex Inoculation Tuberculosis J Mt Sinai Hosp 6 4-30 1939

systemic infection Lowenstein was unable to prevent the generalization of a tuberculous infection from the hindleg of a guinea pig when he amputated the limb five minutes after the inoculation A great number of similar observations have been made[366] showing that a truly local skin infection hardly exists The primary tuberculous complex of the skin is of little practical though of great theoretical importance The majority of the tuberculous skin infections differ in two important points from the primary complex They occur in an already tuberculous and allergic organism and they are overwhelmingly autogenous and usually hematogenous These two facts help to explain many of the characteristics of the tuberculodermas *

The *great variety* of clinical pictures of cutaneous tuberculosis is caused by the fact that neither the virulence of the tubercle bacilli nor the defense mechanisms of the human organism are powerful enough to bring about either a complete healing or a fatal course The tuberculous infection can be compared to a war of position and attrition J Jadassohn believed that superinfection is the most important factor in developing lupus from a tuberculous infection This has been widely accepted though some authors at least in some cases have placed more emphasis on the differences in the reactions of the infantile and adult human skins Volk[366] sees an analogy in the difference of the primary tuberculous skin infection of the guinea pig which almost always develops an ulcerative and later generalized and fatal tuberculosis and the cutaneous infection of the rabbit in which the skin infection resembles lupus remains localized and has a marked spontaneous healing tendency [727]

The *bovine* type of the tubercle bacillus causes about 13 per cent of all cases of skin tuberculosis[728] It has already been said that the *tuberculin skin test* becomes positive from three to eight weeks after the infection The positive reaction is evidence of allergy against the tubercle bacillus and its products but it does not indicate immunity or resistance The complete breakdown of the resistance as encountered in miliary tuberculosis and cachexia may be accompanied by a breakdown of other systemic functions e g the ability to react with inflammation to the tubercle bacillus In other words the tuberculin reaction may become negative This phenomenon is called *negative anergy* However measles influenza and other infections some forms of skin tuberculosis and especially the sarcoids[725, 729, 730] may prevent a positive reaction in an active

* The term tub rculid has been avoided si ce it is confusing and unnecessary It can be considered accepted that all tuberculids are tub rculosis (Sulzberg r and Goodma [725]) a d that microo ganisms are demon trable in practically all tuberculids (Wise and Sulzbe ger[726])

[725] Sulzberger M B and Goodman J Tuberculod rms M Clin North America 20 995-1007 1036

[726] Wise F and Sulzberge M B Yearbook of D rmatology Chicago 1935 The Y a book Publish rs p 373

[727] Kallos P and Kallos-Deffner L L Ueb r All rgie- und Immunität verhältnisse bei Hauttuberkulose Zbl 48 273 98 1933

[728] Di tz J Ueber di Typen d r Tuberk lbacill n (TB) bei Hauttuberkulose Arch f D rmat u Syph 179 360-386 1939

[729] Zi l r and Häm l Hauttube kulose in ihr n Beziehungen zur Tuberkulose inn rer Organe Erg bn d ges Tuberk Forsch 6 435 1934

[730] Pin er M Non-Caseati g Tuberculosis Am Rev Tuberc 37 690 1938

way by production of inhibiting substances which are called anticutins[731, 73] This is called *positive anergy* In such cases the resistance to infection e g with the bacillus Calmette Guérin may be very high[7 1] The conception of positive anergy is based on the noncachectic cases with positive tuberculosis and one of the mentioned conditions especially the sarcoids in which the tuber culin reaction is negative[733, 734]

The methods of skin testing for tuberculin allergy are the same as those used in testing other kinds of allergic conditions

1 The intracutaneous injection[735, 736] This test is very accurate in J Jadassohn s graded quantitative method which consists of the simultaneous intradermal injections of 0 1 c c of dilutions of old tuberculin—Koch (OTK) *in concentrations of 1 1 000 000 1 100 000 1 10 000* and in some cases *1 100* and 1 10 and control saline wheals[733] More often purified protein derivative (PPD) is used This is available in convenient tablets of two strengths which have to be dissolved in 1 c c of diluent One tenth cubic centimeter of fresh first strength solution (0 000 or mg) is injected first If no reaction within 48 hours occurs 0 1 c c of fresh second strength solution (0 005 mg) is injected into the other arm

2 The scratch or abrasion test (von Pirquet)[737] with OTK
3 The inunction of a 50 per cent tuberculin lanolin salve[38]
4 The patch test[739, 740]

For the technique of these te ts the reader is referred to textbooks of allergy and tuberculosi for comparative evaluation to E Friedman M H Black and A L Esser man[741] M Sulzberger and F Wise[740]

The patch test is a convenient and sufficiently reliable method for pre liminary information Urbach[159] advises following up a patch test which is negative after one week with the more sensitive Mendel Mantoux test In all tests the reaction can be considered positive if an inflammatory papule of at least 5 mm in diameter develops The papule reaches its height in forty eight to seventy two hours and then slowly fades Immediate reactions are not specific

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731 Kogoj Fr Hauttuberkulos Ter Zpravy 6 137 189 u franz Zusamm nfassu g 190 107 1034 Zbl 59 508

73 Pinn r M W iss M and Cohen A C Procutins and Anticutins Yale J Biol & Med 15 459-463 1943

733 Mart t in H and Noll R Stati tische Untersu hung n über die Tuberculin Reaction Arch f Dermat u Syph 158 409 1929

Loewy H Boeck s Sarcoid a d Lupus Pernio Diss rtation Breslau 19 1

73 M nd l F Di v Pir ju t sch Hautr aktion und di intravenöse Tube kulint ha dlung Med Klin 4 402-404 1908

736 Mantou C Intrad rmo-Tuberkulin Reaction Münch n med Wchnschr 55 2117 1908

737 Von Pirqu t C Tuberkulindiagnos durch cutan Impfung B rl klin Wchnschr 44 644 1907

73 Moro E Ü ber eine diagnostisch verw rtbare R action d r Haut auf Einr ib ung mit Tub er culinsalbe Münch n med W hnschr 55 216 1908

739 Nathan E and Kallos P Ueber ine epi utan Tub rkulinreaktion bei Hauttuberkulose Klin Wchnschr 1031 II 2392 2393

740 Vollmer H and Goldberg r F W A N w Tuberculin Patch Test Am. J Dis Child 54 1019 1937

741 Friedman E Bla k M H and Faserman A L Tuberculin Tests Am J Dis Child 46 59-65 1933

A *positive reaction* in children under seven years is generally a sign of active tuberculosis Beyond seven years the positive test must be correlated with the clinical picture In adults a positive test does not prove more than the well known fact that almost everybody once in his life becomes infected with tuberculosis In the vast majority of the cases the disease becomes arrested after the primary stage leaving behind an allergy to tuberculin

A *negative tuberculin test* especially the Mendel Mantoux test must with the mentioned exceptions be interpreted as indicative of the absence of a tuberculous infection of more than 8 weeks

Hematogenous Skin Tuberculosis

Skin tuberculosis may develop by ectogenous inoculation into the skin and by endogenous infection The tuberculosis verrucosa cutis of the hands in slaughterhouse workers the postmortem wart and the lupus of the buttocks in small children who sit on the floor of a tubercle bacilli infected room are examples of ectogenous tuberculous skin infection The endogenous infection of the skin plays a more important part Endogenous lupus by contiguity from underlying tuberculous lymph nodes especially of the neck is a common occurrence in countries where skin tuberculosis is more frequent than in America The lymphogenous spread of lupus is known However compared with these ways of infection the hematogenous tuberculous infection of the skin is far more important Foci of tuberculous infection which are capable of releasing tubercle bacilli into the bloodstream are very common Even old calcified lymph nodes may still contain virulent tubercle bacilli as has been shown in autopsies of patients who for many years suffered from hematogenous crops of lupus It is more difficult to explain why there is so little hematogenous skin tuberculosis in view of the frequency of the foci and of the bacilli in the blood than it is to give reasons for the hematogenous nature of many cases of cutaneous tuberculosis It can be considered a fact that more than 50 per cent of the lupus cases are caused by hematogenous infection [742] mostly from pulmonary or lymphatic foci [743]

The *relationship of pulmonary tuberculosis* to *cutaneous tuberculosis* has been the subject of many investigations Pulmonary tuberculosis has been found existing simultaneously with skin tuberculosis especially lupus vulgaris in percentages differing as widely as 8 and 90 per cent An analysis of 300 lupus cases in Münster Germany[744] showed 12 per cent more or less active and 60 per cent inactive pulmonary tuberculosis while in a control group of about 5000 German university students only 1 per cent active and 18 per cent inactive lung cases could be found St Epstein[745] determined 16 per cent as the incidence of active pulmonary tuberculosis in 200 lupus patients In 429 fatal lupus cases visceral usually pulmonary tuberculosis was the cause of death in

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[742] Kressner F Untersuchungen über Hauttuberkulose Würzburg Abh Bd 27 H 3 1931
[743] Rauschkolb J E Tuberculosis of the Skin Arch Dermat & Syph 29 398–408 1934
[744] Wintzer W Lungenbefunde bei 300 Lupuskranken Ztschr f Tuberk 70 54 59 1934
[745] Epstein St Tuberculosis of Lungs in Patients With Sarcoidosis Granuloma Annulare and Lupus Erythematosus Arch Dermat & Syph 42 1 10 1940

48 per cent[746] From these and many other statistics it can be concluded that the incidence of lung tuberculosis in lupus is a high one On the other hand the percentages of skin tuberculosis in very large groups of tuberculous patients has always been found low 0 2 per cent[747] 1 per cent in 27 540 cases[748] less than 2 per cent in 18 000 cases[749] This compares well with many older statistics[366] and seems to bear out the old rule that lupus patients often become consumptive but that consumptives rarely develop lupus While the figures seem to be very low the incidence of skin tuberculosis is still about 2 to 3 times higher in patients with pulmonary tuberculosis than in a comparable normal group Similar tendencies as in the relationship of lupus and pulmonary disease prevail in its relation to surgical tuberculosis Among 275 lupus cases were 16 per cent with bone or joint tuberculosis while among 371 cases with tuberculosis of the bones and joints only 5 per cent had lupus[750] The isolation of tubercle bacilli from the *blood* either by animal inoculation or by culture with the Lowenstein method has recently been more often successful than was held possible before *It is true that many observers could not obtain the same results as* Lowenstein[7 9] The positive findings however carry more weight than the negative ones Kren[5] could show that if blood culture of patients with lupus vulgaris erythema induratum and lupus erythematosus was done more than seven times positive cultures could be found in all cases The frequently negative blood cultures are most likely due to technical difficulties to unfavorable time of testing and to the too small numbers of the investigations In Kren s[5] series the blood specimens up to nineteen different ones from one patient were sent to Lowenstein without diagnosis It is believed that the irregularity of the showers of bacilli appearing in the blood is responsible for the inconstant findings However with or without confirmation[751] of all of Lowenstein s findings the frequent occurrence of tubercle bacilli in the blood of patients with skin tuberculosis is a fact[5 6 116 75 759]

[746]Stuempke G Skin Tuberculosis Causes of Death Arch f Dermat & Syph 183 216 222 194?

[747]Griesbach R Hautkrankheiten bei der Lungentuberkulose mit besonderer Berücksichtigung der Akne Ztschr f Tuberk 57 405-416 1930

[748]Szántó J Skin Disease in Pulmonary Tube culosis Dermatologica 88 17-48 1943

[749]Gáli G Clinical Types of Pulmonary Tuberculosis Associated With Skin Tuberculosis Tuberkulózis 1 253 59 278 ?79 (Hungarian with G man summary) Zbl 47 ?5?

[750]Meye J Tuberkulo e als Orga systemerkrankung Acta tuberc Scandinav 9 67 288 1935 Zbl 65 569

[751]Kolle W and Küster E Tuberkelbacillen im strömenden Blute Deutsche med Wchnschr 1934 I 309 313

[752]Rubin E H Ha matogenous Tuberculosis in Adult Generalized Hematogenous Tuberculosis Am Rev Tuberc 39 557 586 1939

[753]Wilson G S Tuberculous Bacillemia Medical Research Council Special Report Series No 18? London 1933

[754]Mathies n A F Resultate mit der Loewenstei schen Blutkulturmethode bei verschiedenen Formen der Hauttuberkulose Wien klin Wchnschr 45 719 720 1932

[755]Ibuchi T Züchtung von Tuberkelbacill n aus ströme dem Blut Schw iz med Wchnschr 1933 I 307-310

[756]Popper H Bodart F and Schindler W Tuberkelbacillenzüchtung aus d m Blute II Virchows Arch f path Anat 286 615-637 1932

[757]Courmont P Gaté J and Mich l P J Bacillémi tuberculeuse et tuberculose cutané Presse méd 42 497-498 1934

[758]Oro A Sul valore d l m todo Löwen tein per lo studio della bacillemia nella tubercolosi cutanea e nelle tubercullidi Arch ital di dermat 12 3 15 1937

[759]Löwenstein E Tuberculous Bacillemia and Its Significance in Medicin Quart Bull Health Organ League of Nations 4 819-832 1935

The start of cutaneous tuberculosis in the intima of veins was demonstrated a long time ago [29] The distribution of the lesions in the cases of post exanthematic lupus[760] hardly allows any other explanation than general spread by the circulation with selective 'take' in some sites and failure to take in others (see chapter on hematogenous skin infection)

Blood borne infection may lead to all of the well known pictures of skin tuberculosis While hematogenous infection is the cause of the papulonecrotic and indurative types of tuberculosis and of the majority of the lupus vulgaris cases it is much less common in scrofuloderma and only few instances have become known in tuberculosis verrucosa cutis

Cutaneous Tuberculosis

The primary lesion of *lupus vulgaris* regardless whether of endogenous or ectogenous origin is the *lupus nodule* as it is called though it is usually only a *macule* In its early and uncomplicated stage this is a pinhead to lentil sized red or copper colored smooth spot Under glass pressure the spot does not fade and the blanching of the surrounding skin makes it stand out more clearly in a red brownish or dark yellow color In suitable light it is strikingly trans

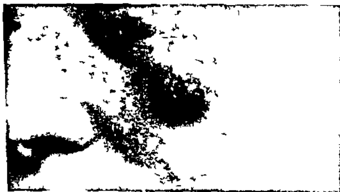


Fig. 95 — Lupus vulgaris (tumidus) (Courtesy Dr M Jessner)

parent which is responsible for the often used comparison with apple butter If one gently tries to penetrate the surface with a fine bulbous probe one is surprised how easily the instrument sinks into the soft tissue at a degree of pressure which would not be sufficient to pierce normal skin Such early lupus nodules are most commonly seen on the face particularly on and around the nose The great variety of pictures which may be encountered during the course of lupus vulgaris can be explained by a number of factors the dominant role of any one being able to create a clinical variety Increase in number and coalescence of the spots may lead to extremely chronic patches of flat lupus which may be as small as a pea or cover entire regions Such large *flat lesions*

[760] Artom M Tubercolosi cutanee post morbillose Arch ital di dermat 9 2 3 23 1933

48 per cent [746] From these and many other statistics it can be concluded that the incidence of lung tuberculosis in lupus is a high one On the other hand the percentages of skin tuberculosis in very large groups of tuberculous patients has always been found low 0 2 per cent [747] 1 per cent in 27 540 cases [748] less than 2 per cent in 18 000 cases [749] This compares well with many older statistics[366] and seems to bear out the old rule that lupus patients often become consumptive but that consumptives rarely develop lupus While the figures seem to be very low the incidence of skin tuberculosis is still about 2 to 3 times higher in patients with pulmonary tuberculosis than in a comparable normal group Similar tendencies as in the relationship of lupus and pulmonary disease prevail in its relation to surgical tuberculosis Among 275 lupus cases were 16 per cent with bone or joint tuberculosis while among 371 cases with tuberculosis of the bones and joints only 5 per cent had lupus [750] The isolation of tubercle bacilli from the *blood* either by animal inoculation or by culture with the Lowenstein method has recently been more often successful than was held possible before It is true that many observers could not obtain the same results as Lowenstein [7 9] The positive findings however carry more weight than the negative ones Kren[25] could show that if blood culture of patients with lupus vulgaris erythema induratum and lupus erythematosus was done more than seven times positive cultures could be found in all cases The frequently negative blood cultures are most likely due to technical difficulties to unfavorable time of testing and to the too small numbers of the investigations In Kren s [5] series the blood specimens up to nineteen different ones from one patient were sent to Lowenstein without diagnosis It is believed that the irregularity of the showers of bacilli appearing in the blood is responsible for the inconstant findings However with or without confirmation[751] of all of Löwenstein s findings the frequent occurrence of tubercle bacilli in the blood of patients with skin tuberculosis is a fact [5 26 116 75 759]

[746]Stuempke G Skin Tuberculosis Causes of Death Arch f Dermat & Syph 183 216 2 2 1942

[7 7]Griesbach R Hautkrankheiten bei der Lungentuberkulo e mit besonderer Berücksichtigu g der *Akne Ztschr f Tuberk 57 405–416 1930*

[748]S ántó J Skin Disease in Pulmonary Tuberculosis Dermatologica 88 17-48 1943

[749]Gáli G Clinical Types of Pulmonary Tuberculosis Associated With Skin Tuberculosis Tuberkulózis 1 953 259 78 279 [Hungarian with German summary] Zbl 47 ?

[7] Mey r J Tuberkulo e als Organ ystemerkrankung Acta tuberc Scandi av 9 67 ?88 1935 Zbl 65 569

[7] Koll W and Küster E Tube kelbacillen im strömenden Blute Deutsche med Wch schr 1934 I 309-313

[7] Rubin E H Haematogenous Tuberculosis in Adult Generalized Hematogenous Tuberculo is Am Rev Tub c 39 557 586 1939

[75] Wilson G S Tuberculous Bacillemia Medical Research Council Special Report S ries No 182 London 1933

[75] Mathiesen A F Resultate mit de Loewensteinschen Blutkulturmethod bei verschiedenen Formen der Hauttub rkulo e Wien klin Wchnsch 45 710 720 1932

[755]Ibuchi T Züchtung von Tuberk lbacillen au ström dem Blut Schweiz med Wchnschr 1933 I 307-310

[754]Popper H Bodart F and Schindl r W Tuberkelbacillenzüchtu g aus dem Blute II Virchows Arch f path Anat 286 615-637 1932

[757]Courmont P Gaté J and Michel P J Bacillémi tube cul u e et tuberculos cutanée Press méd 42 497-498 1934

[758]Oro A Sul valore del metodo Löwenstein per lo studio della bacill mia nella tubercolosi cutanea e nelle tubercullidi Arch ital di dermat 12 3 15 1937

[75] Löwenstein E Tuberculous Bacillemia and Its Significance in Medicine Quart Bull Health Organ League of Nations 4 619 832 1935

Fig 97





Fig 98

Fig 97 — Lupus vulgaris surrounding the ear lobe Exceedingly chronic course not worn off ear lol

Fig 98 — Lupus vulgaris A flat small lesion had been excised and the defect covered by full thickness transplantation Recurrent lupus lesion did not invade the transplant Y ll wi h lesions

are often scaly so that they may resemble psoriasis this is still more likely if the outlines are circinate The tuberculous tissue may grow above the skin level and form elevated hypertrophic and even fungating or tumorlike granulations *Lupus hypertrophicus* lupus tumidus and other terms describe this variety which usually involves the nose the lips and the lobe of the ear



Fig 99 —Lupus vulgaris (Courtesy Dr M Jessner)

Ulceration and crust formation are more often a feature of the hypertrophic than of the flat forms In the latter the ulceration is usually shallow and more marked along the edges The healing tendency and scar formation vary though healing is rarely complete The lupus may spread with an active *serpiginous* edge over large areas leaving in its wake a scar which usually contains some lupus nodules Such annular or gyrate lesions may resemble syphilis or ringworm The face may gradually become scarred shrunken and immovable and the conjunctiva and finally the eye itself may be destroyed The mouth may be reduced to a small rigid hole Such terminal stages may equal leprosy in dreadfulness Cancer is not an uncommon complication The suffering of such patients is beyond description Such cases are fortunately rare especially in America but they can be seen in numbers in all the European lupus hospitals This tragic outcome however is an exception In the vast majority of the cases the lesions are stationary or slowly progressive and often

amenable to treatment Recurrences are very common Spontaneous regression occurs but is rarely complete

The *histology* of the lupus nodule shows a conglomeration of typical tubercles with epithelioid cells giant cells lymphocytes and central necrosis the latter often not particularly marked The same factors which by their dominance decide the clinical picture also produce a great histological variety



Fig 100 Lupus vulgaris (Courtesy Dr Garrett Cooper)

It is now almost generally accepted that *lupus is the expression of a cutaneous tuberculous superinfection* with own or other tubercle bacilli Existing tuberculosis shapes a tuberculous infection of the skin into lupus thus making it a *manifestation of an internal disease* Lupus vulgaris starts in 55 per cent of the cases during the first two decades of life[761] a fact which is not easy to explain Scrofuloderma and children s diseases like measles may play a part though convincing cases are not very common the postexanthematic lupus is a good example of hematogenous lupus[76] It is not too rarely seen to start shortly after or even during the measles and also after other acute exanthems The postexanthematic lupus is often disseminated and appears simultaneously in several or many spots Artom[60] suggests that the anergy during measles favors the development of postexanthematic lupus The prognosis is relatively good since the seeded lesions usually remain inactive[762]

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[761]Zieler K Primary Appearance of Chronic Skin Diseases at Various Ages With Special Reference to Lupous Tuberculosis Arch f Dermat u Syph 183 25-30 194

[762]Leiner C and Spitzer F Uber disseminierte Hauttuberkulosen im Kindesalter Ergebn d inn Med 7 1911

Lupus miliaris disseminatus (Lupus follicularis Tilbury Fox 1878) is a follicular form of lupus which almost always affects the face only It has a great similarity to acne and rosacea In fact most cases go under these diagnoses for a long time After an initial stage of erythema has passed follicular papules develop often with scales a yellow center erythema and subcutaneous nodules The lesions are distributed over the nose the cheeks the chin and though less pronounced the forehead and other parts of the body On close *diascopic inspection* the apparently pustular efflorescences show typical lupus tissue The lesions appear in crops do not coalesce do not contain pus and have a marked healing tendency The histological picture is that of typical tuberculosis The distribution in the perifollicular vascular plexus and other histological findings prove the hematogenous character Tubercle bacilli have rarely been found in the lesions Pulmonary and other visceral tuberculosis has been found in a considerable number of the cases but the tuberculin reaction is often weak The prognosis of the condition itself[763] is favorable and it responds well to peeling with strong ultraviolet light

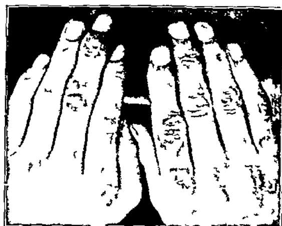


Fig 101 Tuberculosis verrucosa cutis (Courtesy the late Dr W A Pu[illegible] from Sutton and Sutton Diseases of the Skin The C V Mosby Company)

Tuberculosis verrucosa cutis starts as a firm prominent nodule differing from lupus by the lack of transparency and the great resistance to the piercing probe The papules increase peripherally coalesce but little become hyperkeratotic and later verrucous Follicular abscesses are common especially in lesions which have reached more than coin size and greater thickness The patches may reach great size They are frequently seen over the bony prominences of the hands and feet The right hand is most often affected[764] The knuckles and the ankle areas are affected only occasionally The lesions are mostly single or few in number but hematogenous dessemination with many

[763] Peck S M Lupus Miliaris disseminatus fa[illegible] Arch f Dermat u Syph 158 515- 1929
[764] Ledermann K C Statistische Untersuchungen über Tuberculosis verrucosa cutis Arch f Dermat u Syph 167 163 168 193

lesions has been seen There is a decided preponderance of the male sex because the disease is often an occupational infection of slaughterhouse workers who are usually males but occasionally the disease also occurs in other persons who have contact with tuberculous material The occupational character accounts for the common distribution on the hands and feet It also occurs as an autogenous



Fig 109 —Scrophuloderma (Courtesy Division of Dermatology Department of Medicine University of Chicago)

superinfection with the sputum of patients with pulmonary tuberculosis The bovine type of the tubercle bacillus has been found in 50 per cent or more of the cases and bovine infection is probably responsible in all slaughterhouse cases

Volk states that no explanation could be given why in one case tuberculosis verrucosa and in other cases lupus results from superinfection Probably in spite of exceptions the terrain of the hands and feet which has a greater keratotic tendency than other parts is one of the influencing factors This is illustrated

by cases of hematogenously disseminated skin tuberculosis with tuberculosis cutis verrucosa on the acra and lupus on the face [366, 29]

The close similarity of tuberculosis verrucosa cutis and some phases of blastomycosis must be emphasized. Verrucous tuberculosis has a greater tendency to heal than lupus vulgaris and the response to treatment is more complete. The microscopic picture is that of tuberculosis but combined with parakeratosis and hyperkeratosis. Lymphangitis is a frequent complication.



Fig 103 — Tuberculosis cutis colliquativa (scrophuloderma) (Courtesy Dr M Jessner)

Tuberculosis colliquativa (*scrofuloderma*) is a cold abscess of the skin most frequently originating in a subcutaneous tuberculous focus, usually a lymph node or bone. It starts as a subcutaneous nodule which becomes adherent to the skin and forms an abscess or sinus without acute symptoms. Several such lesions may coalesce into a network of sinus abscesses, scars and ulcers, not infrequently surrounded by lupus. The most common site of scrofuloderma is the neck with its great number of easily infected lymphatic nodes. Tuberculosis of the sternum and of the ribs are other starting points for colliquative tuberculosis of the skin. Children and young adults are most often affected. Scrofuloderma occurs occasionally, mostly in young children, in a hematogenous

distribution without connection with underlying structures These cases closely resemble the corresponding phases of sporotrichosis blastomycosis and coccidioidomycosis The prognosis of scrofuloderma and the therapeutic response is usually good though the process may last several years

Ulcerative tuberculosis of the orifices in pulmonary or genitourinary tuberculosis produces characteristic lesions most often found on the tongue and around the anus but also on the lips the ears and the glans penis On the tongue the lesions may appear as shallow jagged oblong round or rhagadiform ulcers the papular primary stage of which is seldom seen The floor of the ulcer is granulated and yellowish the edge slightly undermined The lesion progresses by a coalescence with minute pustular lesions in the surroundings There is little induration and sometimes surprisingly little sometimes surprisingly severe pain Perianal ulcerative tuberculosis occurs in 5 to 10 per cent of patients with pulmonary tuberculosis All abscesses and fistulae in such patients must be considered suspects [765, 766]



Fig 101 —Tuberculous ulcer of the tongue in pulmonary tuberculosis

This ulcerative type of lesion contains more tubercle bacilli than the other forms In line with this fact is the frequent absence of typical tubercular structure and the dominance of nonspecific inflammation Ulcerative tuberculosis of the tongue is more frequently seen in men than in women

Tuberculous ulcers of the orifices are important indicators of visceral especially pulmonary tuberculosis [767-769]

765 Ca n t F [illegible] J C [illegible] la y J [illegible] al Tuberculosis Quart Bull Sea View Hosp 4 445-4 1939

766 [illegible] R M [illegible] Anorectal Fistula Clin North America 17 73 [illegible] 1937

767 [illegible] Au oy R and Mill J W Tuberculosis of the Tongue Report of Three Cases J A M A 95 97 100 1930

768 Nicolas J [illegible] Michel [illegible] Ulcerative tuberculose [illegible] la langue Bull Soc franc de dermat et syph 37 435 43 1930

769 [illegible] Fatto [illegible] Contributo alla [illegible] della tubercolosi [illegible] rosa della [illegible] mucosa Dermosifilog af 7 [illegible] 1941 103

While the forms of cutaneous tuberculosis so far mentioned start predominantly from single lesions the following varieties have in common an

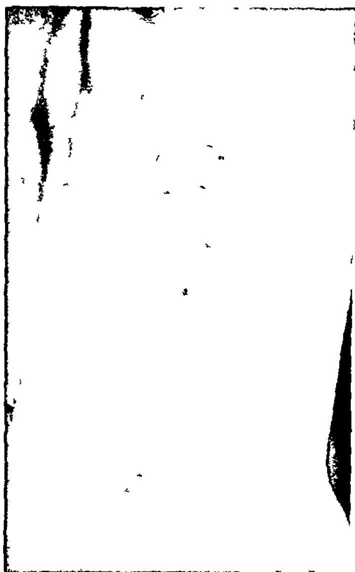


Fig 105 Lichen scrofulosorum (tuberculosis lichenoides) in a lupus patient (Courtesy Dr M Jessner)

exanthematic though not always copious distribution Number and distribution have more importance than the features of the individual lesions which are usually small and not destructive

Miliary tuberculosis of the skin is almost exclusively seen in infants and young children[770 771] In adults the miliary foci are numerous in the subcutis but do not reach the skin The rash consists of pinhead sized hardly prominent often hemorrhagic and slightly umbilicated papules These lesions are quite dense in some areas They may heal spontaneously leaving a slightly depressed pigmented spot The exanthem is inconspicuous and may easily be overlooked[762] The diagnosis is rarely made without biopsy The histologic structure is not so much tuberculoid as inflammatory in character There are tremendous numbers of bacilli Small vessels are sometimes solidly packed with bacillary emboli[76] and surrounded by necrosis but there is a vast misproportion between the number of bacilli and tissue defense[7] The tuberculin reaction is sometimes negative[773] Hoyle and Vaizey[774] list about 16 per cent tuberculous skin manifestations in their series of 120 cases of miliary tuberculosis The prognosis is hopeless

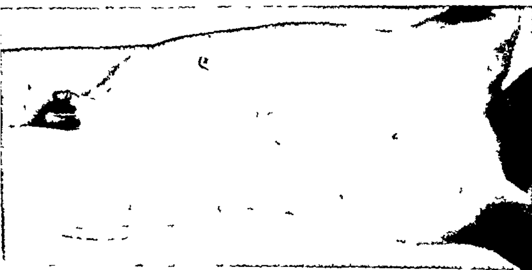


Fig 106 —Lichen scrofulosorum (Courtesy Dr Fri h Urbach)

In *tuberculosis lichenoides* or lichen scrofulosorum large numbers of micropapular mostly follicular often conical and keratotic skin colored or pink to yellowish brown lesions are grouped in round oblong or irregular patches They are mostly found on the back particularly in the lumbosacral region and on the abdomen The lesions develop slowly and patches may persist for years Older lesions often have a scale and if they are packed very closely together in old plaques a large desquamating surface may give a

[770] O ipel P Die Bet iligung der Haut bei Miliartuberkulos Virchows Arch f pa h Anat 284 531-603 193

[771] Koch H Di Tuberkulose des Säuglingsalters Erg i n I inn Med u Kinderh 44 70-98 193

[772] Volk R Hämatog ne multiple subcutan tuberk I ue Abscesse 711 41 6 9

[773] Ned lm n F Tuberculosis utis miliaris acuta g neralisata im Kindesalter Jahrb f Kin l h 131 24 28 1931

[774] Hoyl and Vaiz y Chroni Miliary Tuberculosis Lon lon 193 Oxford University Press

psoriasiform appearance. Usually the center of such plaques is less scaly than the edges but more grater or chagreen leather like. In some cases some or all of the papules bear a hard, sharp, horny little spine. The microscopic picture shows almost invariably tuberculoid structures without or with very few bacilli.

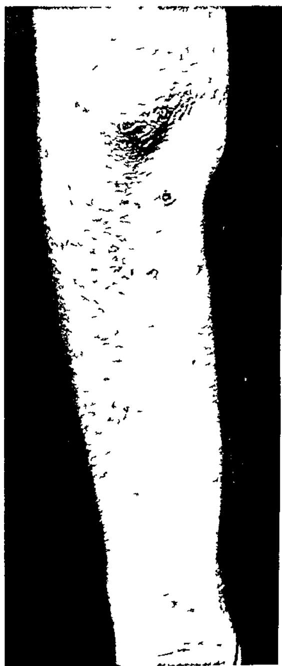


Fig. 10. Papulonecrotic tuberculosis. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Phlyctenular conjunctivitis is a frequent accompaniment The dermatosis is of great[743] symptomatic significance It indicates almost always the existence of internal tuberculosis usually of a more benign type The dermadrome is rare in adults more common in children It frequently makes its appearance after measles and other acute infections However there are great geographic differences Tuberculosis cutis lichenoides is a common sight in the European skin clinics while in North America and particularly in the tropics and sub tropics it is like all types of skin tuberculosis either rare or nonexistent[743, 77] (Pusey after Volk[356])

Tuberculosis papulonecrotica This variety of cutaneous hematogenous tuberculosis has been described under a score of names[356, 7, 8] among which the odd terms folliclis and acnitis are still being used because they were given by the first describer T Barthelemy The term tuberculid is also often applied

The evolution of the lesion is simple and characteristic A cutaneous nodule of linseed size grows within about four weeks to its maximal size which does not exceed that of a cherry stone and becomes a movable firm well defined slightly raised dusky bluish red or brown papule The center of the fully developed papule shows a yellow head which however does not contain pus as one might expect but a rather tough necrotic core which may come out by itself leaving a small punched out ulcer More often a deep necrotic scab is formed which comes off after two to four weeks producing a small crater shaped scar with sharp steep pigmented edges The scars are often more characteristic than the active lesions Papulonecrotic tuberculosis is usually fairly evenly disseminated over the arms hands and legs and occasionally the trunk The extensor surfaces the skin about the joints and the buttocks are more often affected but no area is immune

Genital lesions may suggest secondary syphilis[777] Barthélemy called acnitis a deeper situated acneiform papulonecrotic tuberculosis of the face This condition is closely related to lupus miliaris faciei The lesions of papulonecrotic tuberculosis appear in crops and have a much more marked spontaneous healing tendency than other forms of skin tuberculosis This type of skin tuberculosis is less responsive to tuberculin than is lupus[733] The microscopic structure is tuberculoid Tubercle bacilli are scarce but have quite often been found particularly in children[6]

Combination with pulmonary and other forms of tuberculosis including skin tuberculo is is the rule

Tuberculosis indurata (Erythema induratum Bazin s disease) is a rather rare dermatosis characterized by cutaneous or subcutaneous nodules or plaques of much larger size than in the papulonecrotic lesions There are usually only a few lesions scattered over both legs especially the calves and rarely also over the posterior aspects of the thighs the buttocks the forearms or the face They start as indolent nodules which grow within several weeks to almond or even

[775]Gaban F Incidence of Tuberculosis of the Skin Arch Dermat & Syph 46 130-134 1942

[776]Barthélemy S R L A ... d T Barthélemy Arch Dermat-syphil Hôp St Louis 9 73 310 133

[777]Irgang S Superficial Papulonecrotic Tuberculid in Negro Arch Dermat & Syph. 47 6 636 1943

palm size Such fully developed lesions are visible as a pink or lavender smooth erythema resembling the lilac ring of scleroderma Palpation reveals an indurated plaque of varying depth which is sometimes connected with cordlike phlebitic changes The infiltrate is movable with the skin and usually is not tender In larger lesions the center is depressed or it may though rarely become ulcerated and then resemble a syphilitic gumma The plaques heal spon



Fig 108



Fig 109

Fig 108 —Tuberculosis indurativa (erythema induratum) (Courtesy Dr M Jessner)
Fig 109 Tuberculosis indurativa (erythema induratum) (Courtesy Dr M Jessner)

taneously but the course may take many weeks months or even years if ulceration occurs The oral mucosa is occasionally involved [778, 779] The dermadrome is many times more common in the female than in the male sex New crops are usually observed during the winter and spring [779] The tuberculin reaction is strongly positive Tubercle bacilli are rarely found in the lesions The struc

[778] Tschlachl J Erythema induratum Arch f Dermat & Syph 90 371 1908
[779] Forster A Erythema induratum Arch f Dermat u Syph 153 99 1927

ture is decidedly tuberculoid Combination with visceral tuberculosis and with other forms of cutaneous tuberculosis is not rare [366]

Rosacea like Tuberculosis Lewandowsky[780] described this form of skin tuberculosis which in the majority of cases is seen in women[733 781 78] of 30 to 60 years of age The disorder develops gradually The typical case shows a great number of papules mostly follicular scattered symmetrically over the cheeks and forehead often leaving the nose and chin free The papules are small to medium sized with a decided yellowish brown tinge and do not completely



Fig 110 — Rosacea like tuberculosis (Lewandowski) Note spots which become more distinct under glass pressure (Courtesy Division of Dermatology Department of Medicine University of Chicago)

fade under the pressure of glass The diascope does not however show the transparent apple jelly colored lupus nodule as in lupus miliaris which it resembles There may be some pustulation cyanotic erythema and a certain amount of telangiectasis but not as marked as in rosacea Scaling is sometimes present [366 733]

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[78] Lewandowsky F Rosacea ähnlich Tuberculide des Gesichts Co Bl f schwei Ae zte 47 1 50 1917

[78] Will L J and Crau r F H Rosacea like Tuberculosis (5 Cases) Arch De mat & Syph 31 174 180 193

[7?] Michelson H F and Wi L H Tuberculoid ma of th Fa Arch D rmat & Syph 29 .0-269 1934

[7?] Machee G M and Sulzberger M B Rosacea like Tuberculid of Lewandowsky Arch Dermat & Syph 31 159-1 3 1935

The microscopic structure is tuberculoid No bacilli seem to have been found in the lesions so far The patients are usually though not always[781] highly sensitive to tuberculin which is in contrast to the reaction in lupus miliaris Visceral or other cutaneous tuberculosis mostly of benign character was found in a fraction of the cases Though still rare rosacea like tuberculosis is a relatively frequent form in America[7 5]

Chapter XI

DERMATOSES WITH CLAIMED BUT STILL CONTROVERSIAL TUBERCULOUS ETIOLOGY

Erythema Nodosum

Erythema nodosum* is a uniform syndrome characterized by an acute eruption of cutaneous and subcutaneous nodules together with systemic symptoms especially fever The nodules are mostly found in the tibial areas less often on the extensor surfaces of the forearms and rarely on the face [785] They are not very numerous from a few to about thirty varying from pea to walnut size sometimes moderately raised above the skin level They are quite painful to the touch The more superficial lesions are pink to red and undergo a change of colors which resembles bruises (erythema contusiforme) There is little tendency to coalesce The nodules appear in several crops each of which takes about 1½ to 2 weeks to heal The entire attack may last from three to six weeks or longer Recurrences occur frequently

The outbreak is often preceded and accompanied by fever respiratory and gastrointestinal symptoms and pains in the muscles and joints which are sometimes swollen The prognosis of the dermatosis as such is favorable

The incidence shows a marked preponderance of *children* and adolescents over the adult and of the adult *female over the male* [786] Erythema nodosum is seen more frequently in the *cold season* There seems to be a high susceptibility of the nordic races

There are many reasons to relate erythema nodosum with a tuberculou infection

Tubercle bacilli have lately been detec ed more frequently in the lesions rarely and not [84, 787, 788] undisputedly in microscopic sections but more often by successful inoculation into the guinea pig [787, 789, 790] Debre Mignon Mallet[791]

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* Lit rature up to 19 8 s e P Tachau [84]

[785] T chau P Eryth ta ex udativum multif rme u d Nodo um Handb d H u Gk 6 ? 594 654 19 8

[786] Blu fa l S M and Morri G F Eryth ma Nodosum of Face Arch D rmat & Syph 43 80 804 1941

[787] Milian G a d Brodier I Skin T be culosis R vi w of Rec nt Lit rature Paris méd 1 40 57 1939

[787] Cit ll A R Tuberculou Primary I fection of th Skin and Secondary E yth ma No lo um Arch arg nt de pediat 7 69 85 161 170 1936 Zbl 51 653

[788] Saenz A Ch v llie P Lévy Brühl M and Costil L Su la pré n du bacill 1 Koch vi ulent da les lé ion cutanées et da s l sa g d un malade n plein a c d rythème nou u Co pt r nd Soc de biol 112 951 953 1933

[789] Are a A A F ist ce du Mycobacte ium tuberculosis dan les nodules d l'E yth me nou u Compt rend. Soc l biol 115 340-34 1934

[790] Sa A a d Broca R Récherches bact ri logiques ur l rythèm nou ux Bull Soc franç d l rmat t yph 43 11 1100-1111 1935

[791] D bré R Mignon M nd Mallet R L e am n radiologiqu du thorax au cours d l rythème nou ux Bull oc f ç l l mat t syph 45 11 111 1115 1938

found tubercle bacilli in the lesions in 3 adults and 3 children These authors were unable to detect any pulmonary changes

The *tuberculin reactions* in children and young adults were positive in over 90 per cent and more strongly positive than in control groups [79] There are series of many hundreds of observations available [793 795] In a number of instances the test was known to have been negative before the outbreak of erythema nodosum and was observed to become positive [796 799]

The *provocation* of erythema nodosum [800] or at least of new lesions by tuberculin tests has been reported by Kropatchev and Verzner [801] Wallgren [80] saw erythema nodosum after Calmette Guérin vaccination Yet it should be emphasized that in large series[795] 3 to 8 per cent of the cases have been definitely declared tuberculin negative

Simultaneous manifestations of tuberculosis have been discovered in many instances Prag[793] saw roentgenologic pulmonary changes in 91 per cent of his 157 cases other authors in about 50 per cent [794 801 806] Few writers found the lungs involved in only a minority of their[807] cases [808]

The pulmonary involvement was usually interpreted as recent or primary [79]

A dense and enlarged hilus tracheobronchial lymphadenopathy peri bronchial infiltration pleural exudate or frank hyperplastic tuberculosis are the usual findings The lymph node enlargement was more often bilateral than uni lateral and the pulmonary infiltration was unilateral in about 50 per cent of the affected cases [809] The relatively benign character of the hilar reaction is sometimes shown by its complete disappearance in a short time [807]

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[792]Rotnes P L Eryth ma Nodosum in the Adult Nord med tidskr **13** ?81 88 1937 Zbl **61** 458

[793]Prag A R Erythema nodosum Hygi a Stockholm **91** 9 601 193? Zbl **44** 104

[79]Giertsen C 93 Cases of Erythema Nodosum Acta med Scandinav **82** 87 110 1934 Zbl **49** 346

[795]Landorf N Tuberkulinnegatives Erythema nodosum Acta paediat **17** 180 187 1935 Zbl **51** 288

[796]Comby J A propos de l érythème noueux Bull et mém Soc méd d hôp de Paris **50** 1740-174? 1934 **53** 97?-978 1937

[797]Stavropoulos J Quelques considératio is sur u cas d éryth m noueux Bull Soc pédiat de Paris **33** 585- 90 1935

[798]Béthou I and Berthet F Un cas de primo infection tubercul u avec érythèm noueux ch z une fillette d onz ans Bull et mém Soc méd d hôp de Paris **51** 508 510 1935

[799]Ontaneda L E Rottj r E A and Pasqualini R Q Erythema Nodosum as Symptom of First Tuberculous Infection in Adult Rev Asoc méd arg nt **49** 915-9 1?3 Zbl **56** ?62

[800]Lafosse P Érythème nou ux chez u e tubercul use apr s d injections d tuberculin Rev de la tuber V a 1 461-46? 193?

[801]Kropatch v A N and Ver n V N Eryth ma Nodo um in Small Childr n Sov t pediat Nr **12** 57-65 1936 Zbl **56** 59

[802]Wallgr n A Erythema nodosum nach Calmette-Impfung S en läk tid pp 1393 1395 1932 Zbl **44** 300

[803]Stajic S Erythema Nodosum Srpski arh za c lok l k **35** 146 1?3 1933 Zbl **45** ?9

[804]Gi rts n C Four Cases of Eryth ma Nodosum and Frühi filtrat Acta med Scandinav **82** 55 86 1934 Zbl **49** 347

[805]Hamburg Z tlina F and Kropatschow N Etiology of Erythema Nod sum in Childre Borba s tuberk **11** 11? 115 1931 Zbl **50** 6?1

[806]Saxl O Beitrag zur A tiologi des Eryth m nodosum Arch f Kin J h **92** ?5-301 1931

[807]Paul L W and Pohl E A Eryth ma Nodosum Media tinal and Pulmonary Changes Radiology **37** 131 137 1941

[808]Spink W W Pathog nesis of Erythema Nodosum With Special R f r n to Tuberculosis reptococci Infection and Rh umatic F ver Ar h Int Med **59** 65-81 1937

[809]Kerl y P The Etiology of Eryth ma Nodosum Brit J Radiol **16** 19? 204 1943



F g 111 — E ythema nodo um



Fig 11 Eryth ma nodosum *L ft* ma ked enlarg m nt of th mediastinum and hila lymph odes *Right* four eek l ter There was no d mon trable associated pulmonary disease (From Loppel and Melamed N w England J Med)

The lung changes have quite frequently been interpreted as a primary complex.[804] This is in line with the fact that fresh pulmonary changes are mostly encountered in young individuals. It is of special interest that young adults who by their negative tuberculin tests show that they have so far escaped tuberculous infection are more likely to get erythema nodosum on exposure to tuberculous infection than are controls. These persons usually become tuberculin positive in the course of the disease. This has been demonstrated in student nurses[810] and newly inducted soldiers.[811] *Such and similar cases*[81] *carry much weight* against the argument that a positive tuberculin reaction does not necessarily have to be related to erythema nodosum.[784] If it is true that erythema nodosum is rare in lung sanitariums this could be explained by the fact that most cases in these institutions are no longer in the early stages. Erythema nodosum has been seen to appear in the presence of extrapulmonary tuberculosis, e.g. a cold abscess of the neck[813] or of the breast[814] or after the surgical severing of pleural adhesions.[815]

Tubercle bacilli in the *blood* of patients with erythema nodosum have been demonstrated quite frequently[757, 816, 819] (12.5 per cent Saenz and Broca after Milian and Brodier[786]; L. Nekám Jr.[8 0] in a case of so called typhobacillosis). They do not prove conclusively the tuberculous etiology of the skin lesion since bacillemia is frequent in tuberculosis, but they are a valuable support of a hematogenous pathogenesis.

Tubercle bacilli have been demonstrated in the *gastric juice* especially of children with erythema nodosum[790, 8 1, 8 3] and also in the urine (Ramel after Milian and Brodier[786]). To these findings applies what has been said of the etiologic value of the bacillemia.

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[810] Punch A L Erythema Nodosum Etiology Lancet 2 10 11 1941

[811] Tornell F Untersuchung von Knoten rythemfällen und ihrer Umg bung in d r I ürsorg t ll Sv Nat Tuberk Kvskr 30 3 12 1935 Zbl 52 176

[812] *Debré M R Érythème nou ux et tuberculos Bull Soc franç de dermat et syph* 45 II 1091 1096 1938

[813] Gordon H Case of Tuberculous Infection With Leythema Nodosum Brit J Dermat 45 69 71 1933

[814] P nny W M Erythema Nodosum Brit J M 2 146 1931

[815] Co te F and Bernard J Frythème noueux t néphrit apr s ectio d frid s ch z un tub r culeuse Bull et mém Soc méd d Hôp d Pa is 50 1680 1693 1934

[816] Massini R Tub kelba ill n in *Blut b i Fryth ma nodo um (Negativer I ir u t b i Tuber* kulos u d Fryth ma Nodo um) Verha dl l schweiz naturf Gesellsch p 44 193

[817] Fals eau G Oumansky V a l Ducas P Érythème n ueux et tul erculo e Bull Soc pé liat de Pari 28 5 3 558 1930

[818] Naranjo F Ueber Tuberk lbacilläm i i Fryth ma nol sum in l indesalter Ztschr f Tuberk 71 11 16 1934

[819] Boa F Frythema Nodosum mit Tube k lba ill n im Blut Hospitalstl l 76 868 893 1933 Zl l 47 2 3

[820] Nékám Jr L Fall von Lan louzy sch r Typhol acillo u d Fryth ma no losum Klin Wchnschr 13 1464 1466 1934

[821] Gol lie 5 A Pathog nese les Fryth ma nodosum Monatschr f I I I rl 61 219 67 1935

[822] Wall s of F yth ma Nodosum i 8 hool Chil lre i Nor l med tl l kr 2 493-495 2 48 -488 1931 Zl l 40 781

[823] Phili of Tub cl Ba illi in th Ga tri La ag F om 100 Co secuti Cases of E at 13 393-3 8 193

While the prognosis of the dermatosis itself is good *severe and even fatal tuberculosis* has in a minority of the cases been seen (27 per cent [79], 12 per cent [84], 14 per cent [85]) to follow erythema nodosum

Tuberculous meningitis [796 8 6 8 9] miliary tuberculosis and florid pulmonary phthisis [830] have been reported occasionally The most experienced observers agree that every case of erythema nodosum should be watched until the return of normal temperature and normal sedimentation rate

The Scandinavian writers have often emphasized the *public health* aspect of erythema nodosum [811 831 37] They regard erythema nodosum especially in school children as an indicator of an open source of tuberculosis in the surroundings A school mate [833] a family member or a coworker has time and again been found to spread tubercle bacilli which may account for the tuberculous infection by which erythema nodosum seems to be caused After erythema nodosum children should remain in bed for several weeks and should be kept from school until all danger of acute tuberculosis can be safely disregarded [834]

Small *epidemics* of erythema nodosum in hospital wards boarding school and families [835] have been observed several times and the source of the tuberculous infection has often been found [836 837]

After the remarkable evidence which has been produced particularly by the Scandinavian authors it must be accepted that a varying and often large portion of the erythema nodosum eruptions is due to tuberculosis in the early stages particularly in juvenile at the time of the development of skin allergy [838] The allergic pathogene is finds fresh support in the parallel and more clear cut cases of erythema nodosum in coccidioidomycosis (which see) Here the conditions are less complicated because most of the patients have never been infected and do not come from infected surroundings In coccidioidomycosis the ery

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[8?] Les (F Bo jul n \ a I Cuilial P L pro o ti (l igné d I (yth me nou ux Arch d m d d nf 36 1-30 193?

[82] Eckerst m S (I Erythema no lo um un I Pl u iti ud tiva I d r Kra k ngeschicht der Lung ntuberkulö Acta tul rc Sc dina 6 78 89 193

[8?] Stokes J H E yth ma Nod um and Tube culo Ar h D rmat & Syph 3 ?3-31 19 1

[8?] Merit D v Meni g ale R akti n b I Erythema odo um Monat chr f I ind rh 67 ? 63 1936

Skatmow kl T A tiol gi des Erytl ma nodo um I I Ki d r I ilat pol ka 12 416-4 0 193 Zbl 44 6 6

Les é M F L érythème n u ux chez l enfant Bull Soc fra ç d dermat t yph 45 II 105? 1099 1938

[8?] Cöttch O Fi Eryth ma odo um End mi I ei Spitalalt llu g Mo atschr f ki d rh 85 ?41 58 1933

[8?] Ernberg H Das Knot n ythem et Wa u gsdg al S Nat Tub rk I vskr 30 1 3 193 Zbl 51 661

Land u A Multipl Cases of Eryth m No lo m I a Class of S hool Childr n Arch Dis Childhood 7 8 1932

[8?] B an lo I F H rdma R P an I Bl k W H E yth ma Nodo um an I Tub culosis Cana I J Pub Health 28 37 541 1938

E nberg H Eryth ma N dosum Nord med ti I k 4 30-236 193 Zbl 42 717

[8?] Cillis A Tubercular Etiol gy of Eryth m No losum I v a g i t d rmatosif 25 f 8 193 Zbl 42 60?

Lan lau \ S t ut pil mi E yth ma rod sum S lak tid pr 1419 1420 193 Zbl 45 6

[8?] C ndro A É yth m u t mili I pli mi u Leur apparition fréquent au mom nt I la prin o I t eti tuberrul u Bull t méd Soc méd d Hôp d I aris 47 9? 1931

Lelo g M L éryth m t o ux Faits étiologiques t clini ques Bull Soc fra de d rmat t syph 45 II 1096-1100 193

thema nodosum appears after the primary lung infection has produced allergy. The term "autogenous tuberculin reaction"[839] well expresses the pathogenetic theory. Some authors call erythema nodosum the exanthem of tuberculosis. This too regards the eruption in the light of the general observation that the beginning of the secondary phase of an infectious disease is often marked by an exanthem. The histologic findings sometimes show tuberculoid structure but more often nonspecific inflammation, especially around the veins. The lack of eosinophiles is an argument against an allergic pathogenesis.[840] The scarcity or the lack of tubercle bacilli in the lesions cannot be used as an argument against a tuberculous etiology since it may be explained by the strong defense which has developed and for which the positive tuberculin tests are proof. While especially in children and in cooler climates the important part which tuberculosis plays seems certain, it needs to be emphasized that erythema nodosum has been seen in a great number of other infections,[841] e.g., ulcus molle,[847] lymphogranuloma inguinale, Boeck's sarcoid, coccidioidomycosis, trichophytosis, ulcus vulvae acutum (Popoff 1938 after Pautrier[841]) (Samek and Fischer after Pautrier and Woringer[842]), syphilis, leprosy, measles and rheumatic fever, as well as a drug eruption, and finally without any apparent cause. The knowledge of the varied etiology of erythema nodosum invalidates an argument against a purely tuberculous etiology, namely, the cases which are numerous in some series in which by no method, even by autopsy in some instances, could tuberculous infection be found.[809]

The *variations* in the analyses are remarkable. Poppel and Melamed[843] found in a New York series only 4 out of 88 cases associated with tuberculosis. Ramel[844] believes that idiopathic erythema nodosum is always in the child as well as in the adult the cutaneous manifestation of a tuberculous bacillemia. *It seems best to regard erythema nodosum as a clinical rather than an etiological* entity; however, the important role of tuberculosis, especially in children, cannot be denied.

Erythema exudativum multiforme has been suggested to be caused by hematogenous tuberculous infection.[844, 845] English investigators[846, 847] were unable to duplicate the guinea pig inoculations. The idea cannot be considered established except possibly for some cases of the Landouzy type of tuberculous

[839] Ernberg, H.: Erythema Nodosum and Tuberculosis, Am. J. Dis. Child. **46**: 129-130, 1933.
[840] Grzybowski: Erythema Nodosum, Bull. Soc. franç. de dermat. et syph. **45**: III, 1053-1056, 1938.
[841] Pautrier, L. M., Ullmo, A., and Baum, ...: L'érythème noueux au cours de diverses infection, Bull. Soc. franç. de dermat. et syph. **45**: II, 1071, 1938.
[842] Pautrier, L. M., Woringer, Fr., and Zorn, ...: Erythème papuleux ..., Bull. Soc. franç. de dermat. et syph. **40**: 155-158, 1933.
[843] Poppel, M. H., and Melamed, A. M.: Erythema Nodosum, New England J. Med. **227**: 325-330, 1942.
[844] Ramel, E.: L'erythème exsudatif multiforme, Rapp. Congr. Dermatologistes Langue franç. pp. 59-198, 1933.
[845] Dufourt, A.: Deux cas de typhobacillose avec érythème polymorphe, Lyon méd. 1930 I, 89-97.
[846] Percival, G. H., and Gibson, H. J.: Etiology of Erythema Exudativum Multiforme, Brit. J. Dermat. **93**: 379-31, 1931.
[847] Hallum, R., and Edington, J. W.: Investigation of Alleged Tuberculous Etiology of Erythema Exudativum Multiforme (Hebra), Brit. J. Dermat. **95**: 133-141, 1933.

bacillemia [848] Erythema multiforme and other exanthematic erythemas have been seen in association with erythema nodosum (Debre after Milian and Brodier[786])



Fig 113 —S vere partly l ullous erythema exudativum multifor with typical eryth ma nodo um on the l g To liiti a ute polyarthritis R cu r nt attacks in p i g

Initial Exanthems —In infantile tuberculo is ephemeral and inconspicuous morbilliform roseolar urticarial or erythema multiforme like exanthems on the arms and legs have been observed occasionally by some authors and quite frequently by others They may appear at the transition of the pre allergic into the allergic phase of pulmonary tuberculosis [849 851] i e about two months

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[848] S near F F Cutaneous Tuberculosi and Cen ral Medi al Diagnosi Ann Int Med 8 1 4 1 81 1935

[849] L ff nb im r A Das Erste anth m (Frühexanth m) der Ki idli l Tuberkuloseinfection Mü ch n med Wch schr 74 535–537 19 7

[850] von Mörit D Tuberculotisches Frühexa them Wi n kli W hnsch 1934 II 1091 1093

[851] Kun iratitz K Da Erst xanthem d r ki dlich n Tuberkuloseinf kti n Wi n. klin. Wchnschr 19 8 I 9 1 923

after the infection These exanthems being connected with the early allergic phases have been seen mostly in children They are explained along the same lines as erythema nodosum



Fig 114 —Eryth ma exu lativum multiform (Courtesy Dr M J n r)

Lichen nitidus[85] consists of pinhead sized glossy light colored superficial papules which most often occur on the penile skin The lesions develop slowly and without any characteristic changes They may stay for years The microscopic picture is that of an almost too typical tubercle just below the epidermis with many Langhans cells and little necrosis In a number of cases coincidence with pulmonary or cutaneous tuberculosis has been observed [376] but the tuberculous nature of the dermatosis is still controversial

Granuloma annulare (Radcliffe Crocker) is characterized by hard yellow white almost flat papules arranged in coin sized or larger rings most often on the dorsa of the hands rarely on the arms or elsewhere on the body The course is slow and may become arrested at any stage There are no complications or other changes than spontaneous regression sometimes after many years The microscopic picture shows a deep seated granuloma with central necrosis rarely[853] with a marked tuberculoid structure [854]

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[852]Pinku F ( ) I u k tcher f mig Haut ruption Li h itidu Arch f D mat u Syph, 85 11 190

[853]Rusch (ra ul ma Ann l Zl 1 11 401 13 1

[854]Jacobi F (uloma An ul fla H l H u Gk 10 79–85 1931

J Jadassohn[85] and later his pupils (Martenstein and Knoll[733]) were impressed by the frequently negative tuberculin reactions in granuloma annulare in spite of many facts which pointed toward a connection with tuberculosis They felt that granuloma annulare should be grouped with other positive anergic tuberculous conditions especially Boeck s sarcoid Michael[854] reviewed 86 cases from the literature and found a definitely lower percentage of positive reactions than is found in the population at large Tubercle bacilli have only exceedingly seldom been found in the lesions[855] the guinea pig inoculations being just as unsuccessful as the microscopic examinations Combinations with pulmonary and other tuberculosis has been seen only in 16 to 20 per cent[856] Tuberculin has had a healing effect in a number of cases and has occasionally provoked lesions[857] The strongest argument against a tuberculous etiology is furnished by a number of cases in early childhood without tuberculosis and with negative tuberculin reactions[853 8 9] Granuloma annulare is probably a clinical reaction common to different agents of which the tubercle bacillus i only one Some authors believe in a toxic etiology[860]

Boeck s Sarcoid (Benign Miliary Lupoid)

Boeck s sarcoid is a rare systemic disea e involving predominantly the skin the lungs and the bones

The trouble usually starts insidiously and takes an extremely chronic and unusually benign course The original description of Boeck distinguished three types characterized by small disseminated cutaneous nodules or papules by larger and more grouped nodes and by diffuse sometimes very extensive in filtrated plaque With the greater number of cases published tran itional and other varieties have become known and cases without skin involvement have been recognized It is now believed that the skin participates only in about half of the cases (Vosbein and Bonnevie after Leitner[861])

The clinical feature which connects the nodosities of varying size and shape is the diascopic appearance of small yellowish spots which resemble lupus lesions but are smaller and less transparent These lupoid spots which are responsible for the name benign miliary lupoid may coalesce into larger areas The small nodules are usually numerous giving the impression of an exanthem while the large nodules occur in smaller numbers The lesions which are present simultaneously are in various stages of development In some the skin may still be of normal color while in others definite lupoid red or brownish discolora

[853] Jadassohn J Sarcoid und Lupus pernio Kor Bl Schweiz Aerzte 44 1474 1477 1914
[854] Michael J Etiology of Granuloma Annulare With Special Reference to the Tuberculous Theory Arch Dermat & Syph 29 1 9-705 1934
[855] Epstein F Relationship of Tuberculosis and Granuloma Annulare Dermatologica 85 1 6-10 1 34
[856] Wise F Suggested Tuberculous Origin of Granuloma Annulare Brit J Dermat 41 6 -68 19
[857] Touraine A Etiologie du granuloma annulare Bull Soc franç de dermat et syph 38 84 1931
[858] Williams F Granuloma Annulare Brit J Dermat 47 310 340 193
[861] Leitner J Morbus Besnier Boeck Schaumann Basel 194 Benno Schwabe



Fig 115 —Boeck s sarcoid Ring shape l le ion with atrophic cent r (Court sy Divi ion of Derma tology Departm nt of Medicine University of Chicago)



Fig 116 —Boeck s rcoi l l upoi l appearn e u l gl s pressure (urtesy Divi ion of D rma t logy D partm nt of M li in Uni rsity of Chi ag)

tion has already developed. On the face such mature efflorescences are often bluish red with a yellow border.[633, 56] Other nodules may be regressing leaving a depressed atrophic scaly scar in the center while the periphery is still active, red or brown, sometimes telangiectatic and infiltrated. Such ring-shaped or circinate figures surrounding a thin scar are particularly characteristic on the forehead and other parts of the face. Other typical though less common sites are the shoulders and the extensor surfaces of the arms, occasionally the hands and feet, where the ring form is usually less marked because the center is more apt to stay pigmented. The scalp may also become affected. Ulceration does not occur.

The *lungs* are frequently affected in Boeck's sarcoid.[730, 863, 869, 935] The sarcoid lesions in the lungs are small and disseminated mainly over the middle and lower parts. A diffuse fibrosis with stringy rather dense shadows radiating from the hilus toward the periphery[730] is often noticeable. A diagnosis of Boeck's sarcoid based on the lung picture alone is hardly possible. In cases without skin lesions a diagnosis of miliary or fibrotic tuberculosis, of carcinomatosis or of less specific changes will probably be considered. A characteristic of the pulmonary changes is the chronic course and the fibrotic tendency, which is the analogy of the [illegible] of the skin lesions. In spite of widespread and dense changes of the lungs the symptoms are usually only slight.

This is also true of the *bone* involvement.[869] Nielsen[867] has observed [illegible] cases of Boeck's sarcoid over many years. He and many other authors [illegible] the small bones, especially the terminal phalanges, most commonly affected. Sarcoid paronychia may precede the bone disease.[870, 871] The course is [illegible] and complete regression of lesions could be demonstrated. The lesions are [illegible] round embolic foci of granulation tissue which replace the bone and cause a [illegible] like X-ray picture. Pathological fractures occur occasionally. If the bone is heavily affected the surrounding soft tissues may become swollen and present the picture of dactylitis or spina ventosa. Bone lesions occasionally [illegible] dermatdromes occur in about 20 per cent of the cases.[872] Similar [illegible]

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[863] Boeck, C. Multiple Benign Sarcoid of the Skin. J. Cutan. & G. U. Dis. [illegible]
[864] Schaumann, J. Boeck's Disease [illegible] 33 (63) 1933 [illegible]
[865] Schaumann, J. Lymphogranulomatosis benigna. Nord. med. tidsk. [illegible]
[866] Kuznitzky, E. and Bittorf, A. Boeck'sches Sarcoid mit Beteiligung innerer Organe. [illegible] med. Wchnschr. 62 [illegible]
[867] [illegible] Boeck'sches Sarkoid (Lupus pernio) und Lungenbeteiligung. [illegible] Syph. 167 [illegible] 1933
[868] Nielsen, J. [illegible] Boeck. Bull. [illegible] 1931
[869] [illegible]
[870] [illegible] Sarkoid [illegible]
Jahr [illegible] 1933
[871] [illegible]
[872] [illegible] 1931

have been seen in some instances of lupus vulgaris (F Koch[873]) The different appearance of tuberculosis of the bones is emphasized by Naegeli[874]

Lymphadenopathy is a common feature The peripheral as well as the visceral lymph nodes especially those at the hilus are frequently enlarged Schaumann[864] found specific sarcoid tissue in the tonsils in all of his cases and there is *enough autoptic evidence that practically all organs may become the site of* hematogenous metastases[730] Marked monocytosis sometimes as high as 40 per cent is a frequent though not invariable sign which Pinner[730] believes to be the hematological manifestation of a monocytic proliferation which also leads to the epithelioid granulomata

It seems that sarcoid is relatively frequent in the American Negro[875]



Fig 117 —Boeck's sarcoid (Courtesy Dr M Jessner)

The *microscopic* structure of the lesions is better characterized by the term noncaseating tuberculosis[730] than by the rather vague word sarcoid Dense foci of epithelioid cell tubercles are separated by areas of connective tissue There is no caseation and little or no lymphocytic infiltration surrounding the lesions so that the apt term naked tubercle has been used Giant cells may be found

[873] Koch F Ostitis tuberculosa multiplex cystoides (Jüngling) bei Lupus vulgaris D[illegible] Wch schr 1935 II 910 9[illegible]

[874] Naegeli [illegible] Les altérations osseuses dans la maladie [illegible] Besnier Boeck Bull Soc franç dermat et syph 41 1 18[illegible]26 1934

[875] Nomland R Hematogenous Cutaneous Tuberculosis (Sarcoid) in Negroes Arch Dermat & Syph 30 59 75 1934

According to Pinner tubercle bacilli have been found in the lesions 25 times. This is a small percentage but considering the *law of Jadassohn and Lewandowsky* the scarcity of microorganisms must be expected in tuberculoid structures and cannot be interpreted against the etiology in question. The fact that in a considerable number of instances tubercle bacilli have been demonstrated in the lesions is a good argument for the tuberculous etiology of Boeck's sarcoid. Kyrle[illegible] showed that during the first days of a crop of typical Boeck's sarcoid tubercle bacilli were numerous in the still erythematous lesion. There were perivascular foci of nonspecific inflammation. Around the eleventh day the acid fast bacilli became scarce and epithelioid cells began to group together

Fig. 118. Boeck's sarcoid. (Courtesy Dr. M. Jessner.)

Kyrle, J.: Die Anfangsstadien des Boeck'schen Lupoids; Beitrag zur Frage der tuberkulösen Aetiologie dieser Dermatose, Arch. f. Dermat. u. Syph. 131: 33-65, 1921

On the thirty sixth day the typical sarcoid structure with epithelioid cell tubercles and giant cells was fully developed but no bacilli could be found In the early stages the blood too contained tubercle bacilli[877] (see also Leitner [861])

The tuberculin reaction is negative often even to 1 mg of tuberculin or only slightly positive in the great majority of the cases This *anergy* is much too frequent to be explained by freedom of tuberculosis infection Negative tuberculin reactions have even been found in cases of Boeck s sarcoid with frank tuberculosis [733 734 877 878] Zieler [7 9] however observed that the tuberculin reaction which had been negative in a case of lupus pernio became positive with the



Fig 119 —Boeck s sarcoid (Courtesy Dr M J

outbreak of pulmonary tuberculosis Lupus pernio is closely related to Boeck s sarcoid Pinner [30] calls anergy an essential feature of the disease Reactivity inhibiting substances in the serum so called anticutins could be demonstrated in four out of eleven patients with sarcoidosis which is less often than anergy [73] but probably more frequent than in normal or tuberculous patients In several animals e g rats dogs cat foxes and horses tuberculosis takes much more often than in man a sarcoid like course with epithelioid cell tubercles absence

[877] Martenstein H Sarkoid Boeck und Lupus pernio Arch f Dermat u Syph 147 70 19 4

[878] Jadassohn W L origine tuberculeuse de la maladie de Boeck Bull Soc franç de dermat et syph 41 1344 1347 1934

of caseation, anergy and anticutins in the serum This fact furnishes a parallel which can also be u ed in favor of a tuberculous character of Boeck s sarcoid [878] Finally combination with and transition into frank tuberculosis has frequently been observed St Epstein[745] found progressive pulmonary tuberculosis in about 12 per cent and less active forms in a still higher percentage [879] sometimes with disappearance of the sarcoid lesions Appearance of the first lesion at the site of trauma[880 881] does not necessarily mean ectogenous infection since the trauma may lower the local resistance and attract the bacteria from the bloodstream In this connection it may be mentioned that subcutaneous injections of many



Fig 1 0 —Boeck s sarcoid (Cou t sy Dr Mclam 1)

substances e pecially oils may cause reactive changes of great similarity to sarcoid The majority of the authors now seem to favor a tuberculous etiology of Boeck s sarcoid while dissenting writers among them Kissmeyer [88] who has wide experience with this rather rare disease hold that the disorder is a specific nosological and etiological entity Kis meyer[883] bases his opinion on the too rare and in his opinion not always valid findings of acid fast bacilli on the

[879] Ronches F S rcoid at 1 Tuberculosis—Ca With Autop y Ar h Dermat & Syph. 46 860-871 194

[880] Forster H R a d Wied r L M Sarcoid (Boeck Type) Arch Dermat & Syph 22 343 1930

[881] Coug rot H and Blum P Tuberculose sarcoide hypodermique par corps étrangers à la suite d infectio d vaccin t l erculeux n e lpl t aqueux Bull Soc franç de d rmat et syph 39 1651 16 103

[882] Kissm yer A Contrit ution à l étude cli iqu des sarcoides Bull Soc franç de dermat et syph 41 110 1109 1934

[883] Kissm y A Beitrag u Aetiologi an l Klinik des Boeckschen Sarkoids Hospitalstid 1932 ll 104" 10 0 Zl1 44 337

benign course on a refutation of J Jadassohn s theory of positive anergy and other reasons * Some writers believe that the disease has the characteristics of a chronic bacillary granuloma with features relating it to tuberculosis syphilis and also to leprosy [879 984] while Rabello Jr [885] thinks that tuberculosis leprosy and perhaps still another disease may produce Boeck s sarcoid Arsenic has a distinct therapeutic influence This fact has been used as an argument against the tuberculous etiology

Lupus Pernio —Lupus pernio is closely related to Boeck s sarcoid [861 887] It manifests itself as ill defined cyanotic cutaneous and subcutaneous nonulcerative plaques most frequently found on the nose and cheeks with marked symmetric tendency On glass pressure lupus like spots can be demonstrated This rare and chronic disorder affects mostly adults and is combined with bone alterations which resemble those found in Boeck s sarcoid Histology and marked positive anergy to tuberculin are further links to that disease and thus to tuberculosis [336 34 855 877 886]

Erythrodermia Exfoliativa (Pityriasis Rubra of Hebra)—Universal redness *infiltration and scaling accompanied by lymphadenopathy may be a phase* in many diseases e g leukemia arsenic poisoning psoriasis eczema and many others Jadassohn [887] in an analysis of 18 cases revealed that in at least eight pulmonary and other forms of active tuberculosis were present Since then many such cases have been described [888]

Purpura Hemorrhagica —The whole syndrome of hemorrhagic purpura even purpura fulminans (Gaede et al [889]) may be produced by tuberculous infection Miliary tuberculosis of the spleen seems to be especially predisposing particularly in children [890 891] Cases with a fulminating course of less than one day have been observed The number of cases of mild and severe purpura occurring in many types of visceral tuberculosis is considerable so that coincidence is unlikely Some purpuric spots could be shown to possess tubercular structure [366] This corresponds to experiences with other purpuric infectious efflorescences e g the rickettsioses and bacterial meningitis An old report of a finding of tubercle bacilli in purpuric skin lesions (Beirsemde and River 1906 after Volk[366]) does not seem to have been confirmed more recently

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* Similarly Leitn [36] in a rec nt review interprets the negative tul culin r action against a tuberculous etiology He also questions the validity of some of th po iti e findings of tubercle bacilli

[884] Kissm yer A La maladi d Boeck Sa coi l s cutanées b ignes multiples Préface d J Dari Paris 193 Masson & Ci

[885] Rabello Jr F Do nées ouvell s pou l i t rp étation l l affection d Besni r Boeck rôl de la lèpre Ann d d rmat et syph 7 571 597 1936

[886] Kobayashi F Lupu pernio mit l noch nv än l rung n Jap J D rmat & Urol 31 1 69 1573 Zll 41 113

[887] Jadassohn J Pityria is rubra H bra und ihre B zi hu g n zu Tub rkulose Arch f D rmat u Syph 23 911 1891 24 8 273 463 1892

[888] Barn y R F Pityriasi Rubra (H bra) Arch D rmat & Syph 18 716-729 19 8

[889] Gaed M S and Vaughn J O Milia y Tuberculosi With Purpura in Infancy Am J Di Child 42 869 873 1931

[890] Qui k A J The Hemo h gic Di a es an l the Phy iol gy of H m ta i Springfi l l Ill 194 Charles C Thoma

[891] Weiner J J nd Cart R P A ute Thrombocytopenic Purpura H m rrhagica A sociat l With Tuberculosi (Miliary) of Spleen Spl n ectomy With Recov y *An Surg 113 [illegible]7-61 1941*

Scrofulosis (Scrofula) —Scrofulosis is a syndrome of nontuberculous inflammatory alterations in a child with tuberculosis predominantly of the lymphatic nodes of the neck and of the bones [89] The characteristic combination of swollen or abscessed submaxillary or cervical lymph nodes eczema especially



Fig 121 —Erythroderm (pityriasis rubra) (Courtesy Dr M Jessner)

around the mouth blepharitis phlyctenules conjunctivitis otitis media and rhinitis used to be a most common sight in the pediatric clinics of Europe Scrofulosis is today rare in America[893] and has also decreased in other countries Landis[893] believes that scrofula is an infection with the bovine type of the tubercle bacillus He explains the disappearance of scrofula with the pasteurization of milk The tuberculin reactions in scrofulous children are strongly positive

Avian Tuberculosis —Human infections with tuberculosis of birds usually chickens may lead to severe systemic and cutaneous diseases which have re

[89] Marfan A B La scrofule conception ancienne conception nouvelle Paris méd 11 13 20 1921

[893] Landis H R M The Disappearance of Scrofula Am Rev Tuberc 21 195-201 1930

semblance to all known types of human tuberculosis but do not quite fit into the familiar pictures. Thus aphthous and septicemic, sarcoid, gummatous and ulcerative forms have been described.[366, 894-896]

The diagnosis will rest on the chicken experiment, the positive avian tuberculin test and the bacteriological culture. The cases seem to be rare. However the diagnosis is important since specific tuberculin treatment has been effective in the cure of such patients (Lowenstein and Joannovic quoted by Urbach[894]).

Lupus Erythematosus Chronicus

The term lupus erythematosus (erythemateux) was coined in 1851 by Cazenave in a clear differentiation from other forms of lupus as many destructive dermatoses were called. Cazenave (after the French text given by Paul Rich-



Fig. 12. —Lupus erythematosus discoid.

ter[897]) describes this form of lupus as one which destroys superficially and which does not develop tubercles (which in Cazenave's time meant ulcerating nodules). The relationship of the disease which we now call lupus vulgaris to tuberculosis was then of course not yet understood because our present conception of tuberculosis, which is based on the presence of the tubercle bacillus or its derivatives, did not yet exist. In 1884 Robert Koch demonstrated by culture and animal experiment the tubercle bacillus in lupus vulgaris. After Koch the term lupus became definitely associated with tuberculosis. Despite the fact that Koch dealt

[894] Urbach, E.: Das Krankheitsbild der Geflügeltuberkulose der Haut beim Menschen und beim Tier. Arch. f. Dermat. u. Syph. 157: 360-381, 1929.

[895] Löwenstein, E.: Das Krankheitsbild der Hühnertuberkulose beim Menschen. Schweiz. med. Wchnschr. 2: 808-810, 1931.

[896] Karl, W.: Geflügeltuberkulose. Verhandl. 8. Internat. Kong. Dermat. 2: 69-72, 1930.

[897] Richter, P.: Geschichte der Dermatologie. Handb. f. H. u. Gk. 14: 206, 1928.

with lupus vulgaris only his work had the effect of stimulating research to prove the hypothesis of a tuberculous nature of lupus erythematosus also

The French dermatologists under Besnier's influence generally adopted the tuberculous etiology of lupus erythematosus while the majority of the German authors concerned with the question rejected this theory for a long time Later on the Germans gradually and very reluctantly became more inclined to acknowledge the importance of tuberculosis in the etiology of lupus erythematosus



Fig 1 3 – I pu ryth mato ch ni u

In the le ions of lupus erythematosus the *tubercle bacillus* has rarely been demonstrated with the Ziehl Neelsen stain [29, 898] In several instances acid fast bacilli closely re embling the tubercle bacillus have been found in the sediment from tissues destroyed with antiformin The etiological significance of these findings must be considered doubtful because such para tubercle bacilli have been found in many media and the antiformin method does not permit the differentiation of bacilli originating from the surface from those from the depth In spite of negative control tests in normal skin[899] these antiformin findings have not been acknowledged as an etiologic proof [709, 899]

As far back as 1906 Gougerot succeeded in demonstrating the presence of the tubercle bacillus in the lesions of lupus erythematosus by means of animal inoculation The e findings have been confirmed several times[729, 900] though a great

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[898] Friedlä l r D Th Etiology of Lupus Eryth matodes Special Ref r ce to Tub rculo is J Cuta & Genito-Urin Di 29 417 1911

[899] Vel l F Lupus yt! matodes Caz n e) H ndl d H u Gk 10 1 697 9 1931

[900] Bloch Br an l Fu h H Chro ic Lu Eryth matodes a l Tub culosis Arch f D mat u Syph 116 742 1913

semblance to all known types of human tuberculosis but do not quite fit into the familiar pictures Thus aphthous and septicemic sarcoid gummatous and ulcerative forms have been described[366 894,896]

The diagnosis will rest on the chicken experiment the positive avian tuberculin test and the bacteriological culture The cases seem to be rare However the diagnosis is important since specific tuberculin treatment has been effective in the cure of such patients (Lowenstein and Joannovic quoted by Urbach[894])

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Fig 12 —Lupus erythematosus discoide

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[894] Urbach E Das Krankheitsbild d Geflügeltuberkulose d r Haut b im Mensch n u d beim Tier Arch f D mat u Syph 157 360 381 19 9

[895] Löwenst in E Das Krankheitsbild d Hühnertuberkulose b im M nsch Schweiz m d Wchnschr 2 808 810 1931

[896] Kerl W Geflügeltuberkulose Ve handl O t rrat ko g D rmat 2 69 272 1936

[897] Richt r P Geschichte der D rmatologi Handb f H u Ck 14 2 206 19 8

observations carry as little weight in the discussion of the tuberculous etiology of lupus erythematosus as the successful treatment with tuberculin One should also remember that nonspecific focal reactions have been seen after injections of many substances e g gold milk and other foreign proteins sulphur etc

It is important in the discussion of the tuberculous origin of lupus erythematosus to consider whether or not this condition is *more frequently found in tuberculous than in nontuberculous* individuals The opinions on this are extremely contradictory Goeckerman[914] denies that lupus erythematosus is substantially more frequently associated with tuberculosis (36 per cent) than other dermatoses (32 per cent) The number of authors who believe that lupus erythematosus is a disease of persons with tuberculosis especially pulmonary and glandular is large Ehrmann and Falkenstein[915] claim that tuberculosis could be demonstrated in about 50 per cent of the acute cases of lupus erythematosus in about 80 per cent of the chronic cases of lupus erythematosus with acute exacerbation and in 98 per cent of chronic lupus erythematosus Oros's[903] figures run similarly high Pautrier and Schaaff[916] give 72 per cent The most recent survey is that of St Epstein[745] who examined 200 cases of lupus erythematosus in 7 2 per cent of which active tuberculosis of the lungs could be demonstrated by X ray This is much less than in cutaneous tuberculosis (16 1 per cent) but much higher than in the controls (3 7 per cent) which were taken of the syphilitic patients in the hospital

On the other hand in a great number of cases it has been impossible to produce any evidence of tuberculosis either during life or post mortem Of course the value of such negative findings is always limited because small foci can easily be overlooked The complement fixation tests with the antigens of Besredka Calmette Ponndorf and others did not corroborate the tuberculous origin of lupus erythematosus[91] *Combination with skin tuberculosis* such as lupus vulgaris scrofuloderma or the so called tuberculids has quite often been reported Lewandowsky[09] wrote in 1916 that the reports about the combination of lupus erythematosus and tuberculids had lately become too numerous to be explained by coincidence Since then these reports have multiplied Practically every type of skin tuberculosis has been seen in combination with lupus erythematosus Lupus erythematosus as well as skin tuberculosis being rare diseases the number of reported combinations seem to exceed by far the rate of pure coincidence Urbach[918] saw lesions of lupus erythematosus the diagnosis of which he secured by histological examination develop in the neigh

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[9] Goeckerman W H Lupus Erythematosus discoides chronicus due to Tuberculosis? Arch Dermat & Syph 3 788 801 19 1

[1] Ehrmann S and Falkenstein F Lupus erythematodes Arch f Dermat u Syph 141 408 19—

[1] Pautrier L M and Schaaff Results of Systematic X ray Examination of Lungs in 29 Cases of Lupus Erythematosus Zbl 56 0

[9] Hübschmann K Komplementbindungsreaktion bei der Tuberkulose mit besonderer Berücksichtigung der Hauttuberkulose Die Komplementbindungsreaktion bei Lupus erythematodes Acta Dermat v reol 7 315-319 19

Urbach F Lupus erythematodes in Verbindung mit einer Skrofuloderma Zbl 11 290 1924

borhood of a tuberculous fistula Stuhmer[919] saw true lupus nodules in the scar of lupus erythematosus The rarity of such observations in America may be explained by the fact that cases of skin tuberculosis are only about one tenth as frequent in North America as they are in Central Europe As mentioned before lupus erythematosus is about as common in America as it is in Europe This lack of parallelism seems to indicate that lupus erythematosus in spite of many relations to tuberculosis is governed by another law than true tuberculosis of the skin

Without going into detail it may be mentioned that evidence of similar character as that in favor of a tuberculous etiology has been produced in support of other bacteria syphilis mechanical trauma cold light and other agents

Thus in spite of the great efforts which have been made the role of tuberculosis in the etiology of lupus erythematosus chronicus *remains controversial*

Lupus Erythematosus Acutus

The most important systemic relationship of lupus erythematosus exists in the rare cases in which the dermatosis either starts with an acute dissemination or where an apparently chronic lupus erythematosus changes its character and becomes *acute* (*Lupus erythematosus acutus and lupus erythematosus chronicus cum exacerbatione acuta*)

Transitional cases between all types of lupus erythematosus have been demonstrated They prove the close relationship of the various types

The acute form of lupus erythematosus seems to occur in *all ages* but the majority of the patients are those in the third and fourth decade

The *sex* distribution of the acute forms has the ratio of three females to one male This ratio is based on a review of 100 cases published in the last twenty years

Many factors can change the character of chronic lupus erythematosus into the acute form Known to have provoked acute lupus erythematosus are exposure to sun and to strong artificial light[920, 921] bee stings applied for the treatment of arthritis[923] mosquito bites gold therapy trivial infections like otitis media[924] or such following tooth extraction[9] lymphangitis[923] polyarthritis[926] and physical and mental strain[927] In many cases however the disease apparently begins without any such factors

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[919] Various authors Lupu ythemat sus Symp ium on Argum ts Fo and Against Tub r culous Natu D rmat W hr schr 99 1340 13 6 1934

[920] Roxburgh A C A ut Di minat d Lupus Eryth mato u Five Fatal Cases *Brit J* D rmat 45 9 109 1933

[921] Hofman Lupus ryth matodes Zbl 17 65 19 5

[922] Hess J H Gen ralized Lupus Erythemato us and Intra abd minal Tumor Am J Di Child 28 1 8 131 19 4

[923] Gru tz O B itrag ur Klinik und Hi tol gie d Lupu eryth matosus acutu Arch f *D mat u Syph* 147 5 4 530 19 4

[924] Vail S Path g nes u d path logi h Anatomi les Lupu ryth matodes acutu Mo kov med Z 9 1 9 19 3 Zbl 35 13 1931

[925] Cl rk F B and Wa ock A W Lupus Eryth matosus Acutus Di mi atu Calif rnia & West Med 21 354-357 19 6

[926] Gibson R Fatal Ca e of Lupus Eryth mat su With Post Mort m Brit J D rm t 37 23 19

[927] E gman M F Jr Early Acut Lupus Eryth m tosus Ar h D mat & Syph 35 685-697 1937



Fig 1 4 —Lupus e ythematosu acutus (Cou tesy Dr M Je ner)



Fig 1 5 Subacute lupus eryth matosu n phritl Exac rbation after prolonged exposure to sunlight early in pri g

The *onset* may be sudden with chills, high temperature and all the symptoms of an acute infection. However, there are cases starting with relatively mild attacks of skin eruptions even without fever. Excessive fatigue is an outstanding complaint.

The most constant early cutaneous lesion is the appearance of sharply outlined red patches on the face. These *erythemas* are often arranged in butterfly or bat shape covering the nose and the malar prominences, the ears, especially the upper parts of the helix, the chin and the neck. Here the erythema is often limited to the lower anterior part, the neck V, which particularly in women is exposed to the light. The erythema is often but not always edematous or vesiculous, especially in severe cases. The rash can simulate erysipelas but the symmetry, the development from a number of small individual erythematous lesions, the comparative stability and the course will soon differentiate the two. In the edema the follicles appear more open, creating an orange peel like surface.



Fig. [illegible] Lupus erythematosus acute disseminated after first prolonged exposure to sun in spring. Scalp lesion with loss of hair and wide open follicles.

The simultaneous appearance of lesions of the scalp and fingers is very characteristic. The so called erythema perstans of the face may remain throughout the whole course of the disease. It may disappear and recur. The erythematous eruptions may spread over large areas, even over the whole body surface. Exudative features like vesicles, blisters and crusts sometimes create an eczematous, impetiginous or even pemphigoid appearance. Hemorrhagic lesions, mostly of small size, have often been observed.

In some cases the skin lesions have a more exanthem like appearance, described as a roseola or as a morbilliform rash. Often the skin lesions appear in crops which fade or heal and recur often after intervals of indefinite length. It is a definite characteristic of the dermatosis to center about the nose and neck. Here the lesions are redder, more deeply infiltrated, more constantly observed, and healing with atrophy is more frequent than in other sites.[315] More or less acute oral and tonsillar infections are not uncommon.

In acute lupus erythematosus the cutaneous eruption is *not* the most important part of the picture. It is the syndrome of a severe systemic infection or toxic reaction which determines the picture and the course. Continuous high fever is an almost regular symptom. General malaise and later on prostration and exhaustion are frequent.



Fig 127 — Lupus erythematosus acutus (Patient of Dr S Rosenthal)

Fig 128 — Lupus erythematosus acutus. Detail of face. Note open follicles (Patient of Dr S Rosenthal)

Fig 129 — Lupus erythematosus acutus. Effluvium capillorum during prolonged febrile disease (Patient of Dr S Rosenthal)

Lymphadenitis, arthritis and more often arthralgia without true arthritis are other septic symptoms. The joint pains frequently accompany the acute exacerbations. The spleen is often enlarged.

Nephritis often with a high albumin content of the urine is one of the most constant and often early complications. Retinitis albuminurica has been seen several times. *Hematoporphyrin* in the urine is a frequent finding in acute lupus erythematosus especially in the severe cases. The photosensitizing effect of hematoporphyrin is well established[928]. *Colitis* and *enteritis* often not only cause diarrhea but severe abdominal pain which has caused unnecessary appendectomies in several instances[929]. *Endocarditis* *myocarditis* and *bronchopneumonia* are common and together with renal failure frequently the immediate cause of death.



Fig 130 Lupu e yth matosus acutus Not c nt r of ra h in neck V area (Courtesy Dr M Jes n r)

The *blood cultures* done in a great number of cases of acute lupus erythematosus have usually been negative. Occasionally streptococci were found[929, 930, 931] and very rarely staphylococci and bacterium coli. These and some other findings probably are terminal or incidental. The largely negative blood cultures indicate toxemia rather than bacteremia.

Leukocytosis of 15 20 000 or more has been observed several times but it is the exception. Much more frequently the *white count is low* even as extremely low as 800. It has been emphasized[93] that even complications like pneumonia pleurisy nephritis and endocarditis failed to raise the low white count. The

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[928] B ing F a l Bar witz J Aktinisch D rmatosen H n lb d H u Gk 4 1 1 S 169 1932

[929] Rose F a l Goldberg I C Lupu Fryth matosu Visc ral Lesion of A ute Diss minated Lupu M C N North America 19 333 1935

[930] O trow ki Lupu ryth matodes acutus Zbl 21 138 19 7

[931] ... m n H W Zur Klinik und Aetiologie des Lupus ryth mat d s acutu Mün h med Wchnschr 72 1073 1076 192

[932] Wendt H Lupus Fryth matosus I t rn l Disease Mün h n med W h schr 81 917 1934

granulocytes are the elements which suffer most while the lymphocytes prove to be more resistant so that a relative lymphocytosis may result Aneosinophilia is another frequent and unfavorable occurrence The reappearance of the eosinophiles often accompanies improvement and remissions Purpuric spots petechial showers and thrombocytopenia are recognized features of the syndrome [93–934] Wendt emphasizes that his patients with leukopenia thrombopenia and purpura had not received gold treatment which can cau e similar lesions

Secondary *anemia* is frequent The sedimentation rate is often increased



Fig 131 – Tet chia in lupu eryth matosu acutu

Acute lupu erythematosu i a very dangerous di ease in both its form though the acute exacerbation of a pre existing chronic discoid lupus erythematosus has a better chance to heal or to return to the chronic stage than have the primarily acute cases [899] Out of 100 cases published from 1920 to 1940 at least 76 ended fatally Recovery being rare only a few cases of the transition of true acute lupus erythematosus into the chronic discoid form have been observed [931]

The gross pathologic findings consist of a variety of septic renal pulmonary and liver changes splenic infarcts and muscular and valvular heart lesions [935]

In 111 autopsies in acute lupus erythematosus (Gawalovski[936]) tuberculosis was the sole finding in somewhat more than 50 per cent In less than 50 per cent there were no traces of tuberculosis but usually another bacterial infection was present Other experiences were similar

[933] Rose F a d Pill bu y D M Acut Di minated Lupus Eryth matosus Systemic Disease Ann Int Med 12 951 963 1939

[934] K il H Lupu Eryth matosus n I Its Morphologic Variants With Particular Relation to Syst mi Lupu E yth matosu Arch D rmat & Syph 36 7 9 757 1937

[935] Gulon C M and Adam F C Six Autopsied Cases of Diss minated Lupus Eryth matosus Am J M Sc 205 33 1943

[936] Gawalovski K Lupus rythematodes acutus Ftud ritiqu Acta dermat venereol 10 1-39 1929

It is likely that the twenty cases of erythema with visceral lesions described by William *Osler*[937] in 1904 included cases of lupus erythematosus acutus The outstanding lesions were purpura erythema colic nephritis and arthritis There is little clinical or post mortem evidence of endocarditis

The *Libman Sacks syndrome*[938, 939] consists of a peculiar verrucous endocarditis differing from that in rheumatic fever mainly by the absence of Aschoff bodies The patients are mostly young females Six out of eleven had lupus erythematosus three more only erythema Purpuric symptoms were common Leukopenia and thrombocytopenia occurred Pericarditis, arthritis and nephritis were found in almost every case

It has been pointed out that all the symptoms of lupus erythematosus acutus are rather fluctuating It is likely though not yet certain that the Osler[937] erythema group and the Libman Sacks[938] syndrome and acute lupus erythema to us form an entity which often but not always develops typical dermadromes The fundamental and common pathology of the group can possibly be seen in the widespread vascular lesions of the finer ramifications described by Baehr Klemperer and Schifrin [940] The lesions consisting in capillary dilation endothelial proliferation a peculiar hyaline degeneration thrombosis and extravasation were found in all viscera in about 25 per cent of the cases but they were most frequent in the skin and in the kidneys Glomerular changes of this kind make the thickened capillary wall appear rigid as if made of heavy wire These wire loop lesions which were present in more than 50 per cent of the cases and which have been often confirmed[938, 941, 942] are very striking The authors emphasize that they have not seen them in any other human disease except perhaps in eclampsia Similar lesions were found in horses which had been immunized by frequently repeated intravenous injections of live bacteria especially of the pneumococcus streptococcus group

More recently[943] a new conception based on observations of physicochemical alterations in the fibers and ground substance of the connective tissue has been developed

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[937]Osler W The Erythema Group of Skin Diseases Am J M Sc **127** 1 1904

[938]Libman E and Sacks B A Hitherto Undescribed Form of Valvular and Mural Endocarditis *Arch Int Med* **33** *701 1924*

[939]Belote C H and Reuter H S [?] Lupus Erythematosus—So-called Libman Sacks Syndrome—Relation to Dermatology Arch Dermat & Syph **33** 642 [?] 1936

[940]Baehr G Klemperer T and Schifrin A Tr A Am Physicians **50** 139 1930

[941]Jarcho S Lupus Erythematosus Associated With Visceral Vascular Lesions [illegible] of Autopsied Cases Bull Johns Hopkins Hosp **59** 62 [?] 73 1936

[942]Denzer & Blumenthal Acute Lupus Erythematosus Disseminatus Am J Dis Child **53** 525 [?] 1937

[943]Klemperer P Pollack A D and Baehr G Acute Lupus Erythematosus New York State J Med **42** 2225 194[?]

Chapter XII

LEPROSY*

History

Lepro y has been known in the near and far Orient from time immemorial The Bible is replete with mentionings and ruthless laws of quarantine dealing with a disease called zaraath literally uncleanliness or contamination in the Hebrew original and translated by the sages of the Septuaginta with the Greek word lepra Though there is still some doubt about the identity of zaraath and leprosy the majority of the medical archeologists believe in it From the stern biblical law stems the general fear and the cruel treatment of the lepers throughout the Christian era almost up to our times The numerous lepers of medieval Europe were completely outlawed and excluded from all relations with their fellow men They lived as beggars compelled to announce their approach and presence by loud rattles bells or horns and to take the alms on which they existed in bags on a long stick It is a great merit of the Christian church to have tried to ease the fate of the lepers in many ways especially by the foundation of many leprosaria throughout the western world [9]

The modern history of leprosy starts with the discovery of the leprosy bacillus by Armauer Hansen (1873) an accomplishment to which Albert Neisser contributed in many ways

Geography —At present the number of lepers in the world amounts to about 3 million While the majority of them live in the three main centers of Eastern Asia India and Africa smaller endemic foci exist in many other countries mainly the tropic but also in the United States the Mediterranean Norway the Baltic and Russia Occasional cases appear in the great centers of immigration and world traffic In the United States the disease has probably been introduced by Negro slaves and other immigrants A small epidemic of about one hundred cases was discovered among the Scandinavian immigrants in Minnesota Leprosy is now to a relatively small extent endemic along the gulf coast About *four hundred lepers many of them foreign born live in the modern National*

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* Mainly based on the monographs of Lewandowsky [944] Jadassohn [945] Leloir [946] Neisser [947] Schaeffer [948] Klingmüller [949, 950] E Muir [951]

[944] Lewandowsky F Lepra Handb d inn Medizin 1 2 1231 1261 19

[945] Jadassohn J Lepra Handb d path Mikroorg 5 1063 19 8

[946] Leloir H Traité pratique et théorique de la lèpre Paris 1886

[947] Neisser A Lepra Virchows Arch f path Anat 83 514 1881 84 536 1881 103 355 1886

[948] Schaeffer J Lepra Internat Leprakonferenz Berlin 2 61 106 3 4 1 4 4 1897 Arch f Dermat u Syph 44 159 1898

[949] Klingmüller V Die Lepra Handb d H u Gk 10 2 1 505 1930

[950] Klingmüller V Lepra Übersicht seit 1930 Zbl 57 321 1937 1938

[951] Muir E Leprosy Diagnosis Treatment and Prevention Ed 6 Delhi and Simla India 1938 British Empire Leprosy Relief Association

[952] Grön K Die Lepra in Literatur und Kunst Handb d H u Gk 10 2 806-84 1930

Leprosarium in Carville Louisiana[953] Great numbers of lepers live in the Philippines and in Hawaii where under American administration important scientific observations have been made The leper island of Culion in the Philippines and the Kalihi hospital of the United States Public Health Service in Honolulu have in many ways become model institutions Some authors think that leprosy existed in America before the voyage of Columbus

Etiology, Contagion —Leprosy is caused by the Hansen Neisser bacillus an acid fast rod which in many ways is related to the tubercle bacillus It stains best with the Ziehl Neelsen method but it is a little stouter and straighter more angular if bent and usually more numerous and more apt to form bundles than the tubercle bacillus

Culture as well as progressive infection of animals has not yet been accomplished in an entirely satisfactory and corroborated way Though this has hampered elucidation of many phenomena the etiologic role of the Hansen Neisser bacillus has been sufficiently demonstrated by its constant presence in almost all leprous lesions in the blood in the majority of the organs in about *50 per cent of the cases and in all secretions as well as by its absence in other* diseases and in healthy individuals from leprosy free surroundings

Leprosy is a moderately contagious disease The epidemiology is still contradictory Most individuals according to Muir[954,955] nine out of ten seem to possess a high degree of *resistance* This is demonstrated by many instances of persons who remained healthy in spite of exposure to massive infection over a long period of time These were mostly family members who lived together with contagious lepers Conjugal leprosy is not common and contagion by intercourse occurs rarely Nurses and physicians caring for lepers have not very often become lepers *It is hard to decide how much credit must be given to sanitary measures* and avoiding contact

True congenital leprosy is rare Rodriguez[956] did not find a single case in 871 children born of lepers in the Culion colony Many children in leprous surroundings become infected early in life but many stay healthy[945] Breast feeding is not an important factor in the transmission of leprosy from mother to child[956] Contact with contagious lepers in close living quarters seems the main way of transmission but even under such conditions contagion does not invariably occur The author saw a leper covered with tuberous lesions who *lived for 16 years in one room with his family all members of which remained* healthy

Though experienced leprologists believe that the leprosy bacillus does not live long outside the human body many authors are convinced that the disease can be carried by insects especially bedbugs and acari and a variety of fomites

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[953] Hopkins R and Faget G H Recent Trend of Leprosy in the U S A J A M A 126 93 943 1944

[954] Muir E Importance of Natural Resistance in Leprosy Tr Far East A Trop Med 2 547 193

[955] Muir E Leprosy—Resistance and Typing of Skin Lesions Lepro y Rev 10 1 5 1039

[956] Rodriguez J Leprosy Studies Philippine J S 27 455 19 8 31 11 19 6 J Philippine Islands M A 6 40 1925 6 4 13 6 8 345 19 8 9 447 19 9 Monthly Bull Philippine Health Serv 8 27 19 8 8 702 19 9 6th Congr Far East A Trop Med Tokyo 19 2 639 19 6

among which bedding plays a major role Airborne droplets from coughing and sneezing may carry the microbes [948] but the importance of this way of transmission is controversial The infection of the nose with the fingernails is important Leprosy is mostly a disease of the underprivileged classes intimately connected with dirt poor housing poor diet and other unsanitary conditions

Incubation, General Course, Types—The incubation period is extremely variable the observations ranging from one week to as long as 32 years The average may be one or a few years Rodriguez [956] in observations of children of lepers in Culion, found it to be three years nine months The course of the manifest disease itself is extremely variable with regard to severity of symptoms type of prevailing lesions acute attacks remission complications and final outcome In spite of all variations and transitions three definite clinical types stand out

Lepra lepromatosa (tuberous cutaneous leprosy L type)

Lepra nervosa (anesthetic neural leprosy N type)

Lepra mixta (L plus N type)

Lepra maculosa is not a type but rather a stage which may be encountered in any of the three types One or the other type is usually predominant in an area e g neural leprosy in China The general rule that the neural type is more common in the tropics and the lepromatous variety in the temperate climates has many exceptions

The Clinical, Especially Cutaneous, Symptoms of Leprosy

The Early Stages The *primary* skin lesion is a round pink tan copper colored or whitish smooth usually single macula of about 1 cm which grows slowly up to several centimeters in size and may remain stationary over a long time The surface is glossy and the edge slightly raised Later when the periphery grows the center appears depressed or even atrophic Frequently there is a depigmented areola *Depigmentation* more pronounced in the colored skin is often the most noticeable element [96] Sooner or later *nervous* signs and symptoms in the affected area start A period of hyperesthesia or numbness[953] may precede the anesthesia While the sense of temperature is most often the first to be disturbed after a short time touch and pain and later the sweat secretion become equally impaired The primary lesion is rarely an object of medical attention It is hardly ever seen in the leprosarium in Carville La (Personal communication to the author) The best observations of initial manifestations were obtained by Rodriguez[956] among the children of lepers in Culion in the Philippines The primary lesions may look very trivial especially in the colored skin which becomes easily depigmented after scratches and banal pyogenic infections However the detection of anesthesia establishes the diagnosis of leprosy Bacilli are not very numerous in the primary lesions Rodriguez[956] found that the commonest initial sites were the buttocks the cheeks the posterior and lateral surfaces of the thighs and the loins The experiences of other observers are similar [93] The primary lesion was never seen on the chest or the abdomen a frequent site of later lesion

The primary sore is often found on the *nasal mucosa* Here it may appear as an ulcer of the anterior septum causing epistaxis which is a well known early symptom Bacilli may usually be found early in the nasal mucus Mouth and tonsils are other portals of entry

Some authors believe that leprosy may develop without a primary lesion In other cases nervous manifestations may be the first signals of the infection

Since the primary lesion is frequently inconspicuous and without subjective symptoms the *diagnosis of leprosy is usually made after its generalization* which occurs through the bloodstream and the lymphatics



Fig 13 —Leprosy Early pigmented and depigmented macula (Courtesy U S Marine Hospital Carville La)

The following types of lesions any of which may be noticed first represent the most characteristic elements of *early generalized leprosy*

1 *Erythematous maculae* of bluish or pinkish hue which in their early stages fade on pressure The red spots start as small round lesions of less than 1 cm in diameter but they grow multiply coalesce and form gyrate patterns The later appearing lesions grow quickly The individual lesion may disappear without any sequelae or may leave the skin pigmented or depigmented Depigmented areolae and shift of pigmentation make them resemble primary lesions especially when greater activity causes infiltration The red spots are found on the face on the ears buttocks the extensor surfaces of the extremities and sometimes on the back A fine dusty desquamation may be seen on the early maculae [957]

2 *Pigmented maculae* which may be primary or develop from erythematous macules At first they look like freckles or chloasma later they may grow to

[957] Chiyuto S and Velasco F Leprosy Monthly Bull Philippine Health Serv 11 547 1931

hand size Their distribution is that of the red spots Sometimes they form gyrate or variegated patterns There is neither infiltration nor desquamation In their usually extremely chronic course they lead to nervous leprosy

3 *Depigmented maculae* (White spots) which have no or only slightly infiltrated edges They are not completely devoid of pigment but relatively light especially in the colored skin The earliest white spots are perifollicular with slight follicular keratoses They are 1 to 10 cm in diameter sometimes numerous and arranged in large network like patterns thus resembling tinea versicolor or vitiligo Vitiligo however has more distinct borders and the depigmentation is more pronounced Sooner or later anesthesia loss of hair anidrosis and other symptoms of nervous leprosy become manifest The lesions may acquire an infiltrated active margin Sometimes they become the site of vesicles or bullae They may heal with scars

4 *Local swellings infiltrations and nodules* in early leprosy are often first noticed on the alae nasi the ear lobes the elbows and the knees They usually develop in or close to the red spots and may become large plaques They may be few in number or abundant The cutaneous nodules vary from pinhead to walnut size At first the surface is greasy and smooth later dry and scaly resembling psoriasis They often appear in crops accompanied by fever and other general symptoms They grow fast but their growth may become arrested in any stage and there may be no change for years New nodules may appear around the old ones which may heal with a scar Some nodules or deep painful *ulcers* especially under unsanitary conditions occur on the exposed areas of the skin The ulcers may destroy tendons and muscle and the scars may lead to serious contractures and deformities and to strictures of the upper air passages

Anesthesia at first only for heat and pain later for touch is common in the nodules The bacilli are numerous

5 *Blisters* and bullae of all sizes may appear on white or red macules or on the normal skin and may form torpid ulcers The blisters are rare as early symptoms Early microvesicular eruptions which microscopically proved to be lepra were seen in the Philippines in 16 of 40 children [95]

6 *Nervous disorders* especially disturbances of sensitivity may occur early and are *not restricted to the visible lesions* Numbness a leather glove feeling itching and other *paresthesias* especially along the extremities may become very annoying [96] *Hyperesthesia* may make the patients move slowly to avoid any touch They may be unable to turn a key because *the pressure of the* key against the fingers causes severe pain This phenomenon has been called the sign of the key by a leprous doctor who discovered it in himself

Pain on percussion of the bones especially the clavicles the olecranon and the skull is often early and pronounced The deep structures of the foot may be very painful on extension of the ankle joint

Anesthesia a most important sign may develop in connection with visible lesions or independently in apparently normal skin Rodriguez[956] found leprous anesthesia fickle and variable and he failed to find anesthesia in cutaneous lesions in 16 per cent of the cases The legs dorsa of the feet forearms hands and

fingers in the order named are the most frequent sites of anesthesia.[956] Frazier[958] emphasizes the peculiar dissociation of the elements of sensation. The perception of temperature disappears first. Then follows anesthesia for pain and finally for touch.[958] Anesthesia of the little finger, especially of the left little finger, has often been mentioned as an early symptom. Early anesthetic areas are often found on the ulnar aspects of the forearms and hands and on the lateral surfaces of the lower legs and feet. The nervous disorder may appear on all kinds of macules, and trophic ulcers may develop in all anesthetic areas. The superficial nerves, most often the ulnar nerve, the peroneal and the auricularis magnus may early become thickened and palpable. *Atrophy of the musculi interossei* and of the hypothenar eminences are further early nervous symptoms.

7. *Anidrosis*, especially of the finger tips, is an early symptom and may precede anesthesia. Some disturbance of the sweat secretion can be demonstrated *in 70 per cent of the cases (Degotte after Fellner[959, 960])*.

8. *Discoloration of the skin.* The skin often becomes gray or brownish. This is especially conspicuous in the white race. The colored skin has a tendency to become lighter. The skin sometimes takes on a senile and wrinkled appearance.

9. *General symptoms.* Chills, fever, anemia, nausea, weakness, muscular pains and other general symptoms of bacteremia and toxemia are very common. The fever may be accompanied by profuse sweating during which the patient may notice that parts of his body remain dry.

Lepromatous Leprosy.—In the lepromatous form the maculae show an early tendency to become infiltrated or nodular. Nodules may appear in varying numbers and sizes, often on apparently normal skin, without any inflammatory halo. *The first stage may look like an acne papule, then the lesion becomes firm,* shotty, raised and glossy, often with small telangiectasias. The color is pink in the early stages, later purple, brown, copper or bronze. If regression occurs the epidermis of the lesions may peel. The lepromas are often warmer to the *touch than the surrounding area. Hyperesthesia and anesthesia are observed* in almost all cases, but the time of appearance and the site vary. If cut, the patient may feel the touch of the knife but no pain. The lesions may coalesce and form plaques. Such large or small infiltrations may remain stationary for a long *time and then resume their growth or undergo regression or ulceration which* may partly by secondary infection reach a great depth and width, especially in tropical countries. The ulcers may finally heal with scars which reflect the degree of destruction. All stages—infiltration, single and coalescent nodules, *ulceration and scarring—may be encountered in the same patient at the same time,* so that an exceedingly multiform picture results. The face is the main site of the nodular changes. The forehead, the eyebrow region, the nose, the chin, the lobes of the ears and finally the entire face may become involved. The *development of the lepromas on the face is determined by the fibrous and muscular* structures. The fibrous strands crowd the infiltrates together into bulging tumors

[958] Frazier, C. N.: Leprosy: Epidemiology and Natural History, J.A.M.A. 123: 466, 1943.
[959] Fellner, M.: Leprosy—Review of Literature for 1940, Dermatologica 84: 1, 1941.
[960] Fellner, M.: *Leprosy*, Dermatologica 80: 1, 1939.

and divide them by deep creases Thus the lion face the *facies leonina* of advanced tuberous leprosy results Patients in this stage have an amazing similarity It may be difficult to tell from the face whether the patient is young or old man or woman or even whether he is colored or white since the colored skin often becomes lighter and the white skin darker The nose becomes swollen partly by specific involvement of the nasal mucosa which may lead to complete destruction of the septum with subsequent collapse of the nose It is surprising that the sense of smell resists destruction for a long time Corresponding lesions appear in the mouth the pharynx and the larynx There are infiltrations ulcerations and scars with resultant deformations and strictures The *eyes* become involved in nine out of ten fully developed cases The scalp and Scarpa s triangle often remain free and the trunk generally is not as heavily involved as the face The buttocks are common sites of large nodular plaques



Fig 133 —l pr matou l prosy (C urtesy Divisio of D rmatology D partm nt of Medicin Univ rsity of Chicago)

Involvement of the *lymphatics* causes elephantiastic changes especially of the lower legs with all the complications of the syndrome such as recurrent erysipelas and fever ulcerations and finally mutilations The external genitalia are commonly affected Every internal organ may take part in the process though with great variations In some cases the gastrointestinal symptoms dominate the picture in others respiratory or urinary complications dominate The *course* u ually stretches over many years even 2 or 3 decades although acute cases with exanthematic eruptions of lepromas on almost the entire skin

severe prostration of typhoid type and rapid fatal outcome are known. The chronic course is more or less often interrupted by acute febrile episodes, the lepra reactions or *acute attacks*, which contrast strangely to the otherwise extremely chronic course. If the reactions are long and relapsing they may precipitate the outbreak of lepromas and aggravate the course. On the other



Fig 131 — Leprosy. Lepromatous eruption. (Courtesy U S Marine Hospital, Carville, La.)

hand, however, short reactions may exert a healing influence. Urticaria perstans-like lesions of comparatively transitory character have often been seen to appear during the lepra reaction. Existing lesions may become edematous, erysipeloid or vesicular, indicating a severe focal reaction. Remitting fever, arthritic pains and general swelling and tenderness of the lymph nodes may accompany the reaction. The sedimentation rate is increased. The lepromin reaction (see below) is negative.

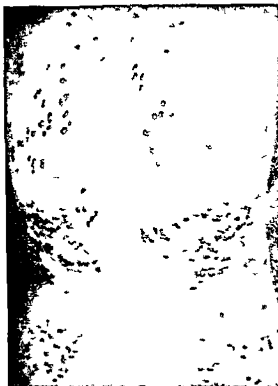


Fig 13 —Lep o y papular exanthem (Cou tesy U S Marine Hospital Carville La)



Fig 136 Leprosy Leproma (Courtesy Dr E R k ll rt rg r)

J Jadassohn[960] was the first to interpret the lepra reaction as a phenomenon of allergy to the leprosy bacillus This opinion is today widely accepted[961] Between the attacks periods of relative well being and regression of the lepromas may set in making the patients hopeful and believing that they are on the road to recovery This hope is however too often deceptive Suddenly fever herald



Fig 137 —Advanced lepromatous leprosy (Courtesy U S Marine Hospital Carville La)

a new outbreak with the appearance of new or the enlargement of old nodules If the patient live long enough the healing tendency become more pronounced and gradual transition into atrophy and scarring may reach an *arrested state* which amounts to healing Actual spontaneous and relatively sudden healing with regression of all lepromas occurs occasionally In such favorable cases the bacilli disappear from the nose and after long observation such a patient may be considered healed according to our present knowledge The neural form is more likely to become arrested than the lepromatous variety but arrest or healing is the exception in both types Ordinarily the patient is condemned to a long period of increasing suffering The involvement of the air passages and the eyes the loss of voice the general induration and infiltration of the skin the nervous disturbances the pain the effort connected with the slightest movement the terrific odor diarrhea and many other afflictions among which the mental suffering of being an outcast is not the least must make death appear as a salvation Pulmonary *tuberculosis* is a frequent complication and cause of death in advanced lepromatous leprosy

[961] Pardo-Castello V and Tiant F R Leprosy Correlation of Its Clinical Pathologic Immunologic and Bacteriologic Aspects J A M A 121 1264-1269 1943

Neural Leprosy.—Lepra nervosa generally takes on a still more chronic course than the tuberous form. Cases of 60 years duration are on record and long periods of apparent arrest may occur.

Fever and other general prodromes herald the cutaneous eruptions more frequently than in tuberous leprosy.



Fig. 138. Neural leprosy. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

In the early stages the appearance of all three types of maculae, the red spots, the pigmented spots and the white spots, dominates the picture, with a conspicuous absence of infiltrations and nodules. The distribution is usually fairly symmetric but varying in size and shape. Symmetric erythema nodosum-like eruptions occur. The spots become anesthetic within a few days. Blisters are common and may predominate so that a pemphigus-like picture results. However, Nikolsky's sign is negative. The bullae may increase peripherally surrounded by an inflammatory vesicular areola. Large bullae may form destructive foul ulcers which heal slowly. The ulcers are painless. In some cases no actual bullae develop but the epidermis forms a dry, scaly crust of yellowish brown color. The predominantly bullous and ulcerative type of

leprosy is called *lazarine leprosy* The content of the blisters contains many bacilli but the tissues are able to destroy them quickly so that they cannot be found in sections The lepromin reaction is positive indicating good defense The prognosis is relatively good [961]

Paresthesias hyperesthesia and anesthesia are the common complaints of beginning neuritis muscular atrophy paralysis and trophic ulcers follow later Some of the nervous complications which predominate in lepra nervosa have already been described



Fig 139 —Lazarine leprosy (Courtesy U S Marine Hospital Carville La)

The affected nerves often become thick spindle or rosary like so that they can be palpated Sometimes only a relatively small area of the skin becomes anesthetic and the whole process may become arrested at this stage and stay so for a long time with no other symptoms until new similar crops continue the development

Anesthesia the most characteristic phenomenon of nervous leprosy leads to ulcers and to mutilation The feet lower legs hands and forearms are most commonly affected Beginning at the little finger the anesthesia may involve the whole arm in similar fashion a leg may become anesthetic Later on symmetry is pronounced It must be stressed that anesthetic areas are not sharply bordered and that they do not exactly correspond to the nerve supply

The successive impairment of the senses of heat cold pain touch and pressure has been mentioned earlier Deep muscular and joint perception remains intact The mucosal surfaces may become anesthetic too The scalp is seldom involved

Muscular atrophy usually starts in the small muscles of the hands leading to a clawlike contracted hand which can hardly be moved Similar sequelae develop *in the feet After an initial increase the reflexes disappear Neuralgic* pains in the trigeminus area are common While total paralysis of the facial nerve is rare the muscles which close the eyes are *frequently* paralyzed Lagophthalmus ectropium loss of eyelashes and dryness of the conjunctivae finally lead

to the characteristic rotunditas oculorum which since the middle ages has been known to be characteristic of the leper The empty stare of such eyes together with partial or total immobility of the face creates the typical *facies antonina*

The skin as already mentioned generally becomes wrinkled ashen or pigmented Gradually the sebaceous glands disappear The nails may partially or totally atrophy and disappear



Fig 140 Leprosy Mutilation (Courtesy U S Marine Hospital Carville La)

Mutilations follow anesthesia The destructive process may start with an abscess or trophic ulcer Resorption of bones especially of the fingers may be a factor The middle phalanx may disappear first so that by contraction the first and third phalanges become drawn together Ainhum like strangulations are another feature All the processes anesthesia muscular atrophy trophic ulcers bone resorptions secondary infection and gangrene may finally lead to the complete loss of fingers toes hands feet and even whole extremities

It is not surprising that mutilation and all the other sequels of the nervous involvement finally lead to cachexia It is however most amazing that life

frequently continues for long years in spite of such destruction and suffering in which the body is dead before the patient dies (Danielssen after Klingmuller)[949]

Lepra mixta combines features of both types It is in some regions more common than the tuberous or nervous forms

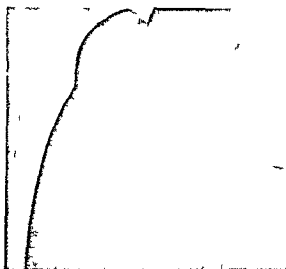


Fig 141 —Leprosy Mutilation (Courtesy Dr E R Kellersberger)

Tuberculoid Leprosy (J Jadassohn[94]) —Besides the lesions of lepromatous and neural leprosy one may encounter round or gyrate flat smooth slightly discolored skin lesions which may be large or small The center is usually depressed and the edge slightly raised Often especially in the edge small lupoid soft nodules can be demonstrated which under the pressure of glass leave a yellowish spot These show little resistance to piercing with a bulbous probe Anesthesia is not very marked but some authors found tuberculoid lesions very frequently in the neural type (Lowe et al after Wilcocks[96] Ota and Sato after Klingmuller[949]) Some of these cases have sarcoidal features[895] It seems to be quite certain that tuberculoid leprosy does not occur together with lepromas[963] at least this combination must be very rare Tuberculoid leprosy is of greater theoretical than clinical importance because its tuberculoid structure and paucity of bacilli demonstrate the so called law of J Jadassohn and Lewandowsky according to which tuberculoid structures are apt to appear where microorganisms or their products are destroyed by the local immune biologic reactions (see page 180) * In other words the immune biologic defenses in tuberculoid leprosy are excellent which is in line with its relatively benign course (see also lepromin reaction)

These cases are generally rare though quite frequent in some small localities They are more often seen in the Negro[945]

* Sulzberger revised formulation with omission of the word rapidly since relatively slow destruction seems likely to produce tuberculoid structures

[962] Wilcocks C Summary of Recent Abstracts (Leprosy) Trop Dis Bull 40 809-815 1943

[963] Büngeler W Allergic Reaction in Tuberculoid Leprosy Klin Wchnschr 19 299-302 1940

Mucosal Manifestations —

The mucosae of the upper air passages are in almost all cases involved though in widely varying degree[964] The *nose* though rarely affected in neural leprosy has been found involved in the lepromatous variety in 33 to 96 per cent according to a great number of authors from many countries The nasal mucosa is often the first site of lepromatous lesions and bacilli can often be found in the nasal discharge when no other symptoms exist The vestibule which may be filled with crusts which have formed over ulcerating lepromas in the nasal mucosa proper *is often the site of the same sequence of changes which takes* place on the skin i e inflammation infiltration ulceration and scarring The infiltrates appear as tough yellowish pink pinhead to cherry stone sized granulations which soften and ulcerate quicker than the corresponding skin lesions The place to look for the lesions is the cartilaginous septum the vestibule and the lower turbinates Perforation of the nasal septum occurs in about 40 per cent of all types



Fig 14 Tuberculoid leprosy (Courtesy U S Marine Hospital Carville La)

Oral infiltrations consisting of grouped small yellowish pink nodules are often found on the *palate* The pharyngeal reflex is lacking in 60 per cent

[964] Pinkerton F J Leprosy of Upper Respiratory Tract Tr Sect Laryng Otol & Rhin A M A pp 97 115 1938

of the neural cases (Belowidon after Klingmuller[949]) Scarring results in deviations of the uvula The gums the tonsils and the labial mucosa are less often involved The lips become more often affected in the skin and vermilion parts than in the mucosa proper



Fig 143 —Leprosy Lepromas of the palate (Courtesy U S Marine Hospital Carville La)

On the *tongue* lepromatous lesions occur as flat yellowish or silvery glossy or tendinous discoid polygonal or streaky nodules or as diffuse infiltrations of the base of the tongue Generally the tongue resists the lepromatous involvement longer than other parts of the mouth The incidence of leprosy of the tongue given in various statistics from different countries varies from 5 to 50 per cent The same type of conglomerations of yellowish pink granulations as are found in the oral cavity occurs on the epiglottis and in the arytenoid area while the vocal cord usually resists for a long time The trachea is rarely affected and if so in the uppermost part

The *lungs* may become lepromatous but this is relatively rare

The eye is very often affected in Norway in almost 100 per cent of the lepromatous and in 60 per cent of the neural cases The percentages of other countries are smaller but still considerable *Lepromatous involvement* of the lids madarosis specific conjunctivitis ectropion keratitis iritis episcleral lepromas lagophthalmus and its sequelae muscular disorders atrophia bulbi and many other lesions are well known[103]

The *auricle* especially the earlobe is a common site of lepromas while the ear duct usually stays free The internal ear is hardly ever affected

The *sebaceous* glands seem to be more active so that the skin over the lepromas is other than normal On this phenomenon was based the *medieval* water test If the skin did not become wet from water the patient was assumed to be a leper

Perspiration may within the affected areas be increased in the early stages and then paralyzed The loss of perspiration may be due to specific destruction of the sweat glands or to nervous disturbance

The *hair* of the body and the beard may early become dry brittle and thin The early loss of the lateral third of the eyebrows has often been emphasized The hair of the head is as a rule surprisingly resistant even in advanced cases but is lost in the affected areas

Heller [558] in his monograph on the diseases of the *nails* reports thinning longitudinal grooves and shedding Occasionally the nails withstand the advance of the disease surprisingly well so that normal nails can be seen on severely affected fingers of mutilated hands Complete and permanent loss or reduction of the nails to tiny horny cones are characteristic of the terminal stages

Pathological Histology —There are three types of pathological changes caused by the leprosy bacillus the infective granuloma the nonspecific inflammation and the tuberculoid structures (Lewandowsky after Klingmuller) [949] Furthermore the Hansen bacillus may be found in tissues without causing any changes The *lepromatous* changes start most often in the walls of the vascular plexus surrounding the follicles the arrectores pilorum the sweat glands the central vessels of the papillae and the cutaneous nerves These early localizations are indicative of a hematogenous infection The infective granuloma consists of lymphocytes plasma cells epithelioid cells and giant cells Usually the lepromas contain great numbers of bacilli arranged in bundles or loose groups between the cells in the capillaries of the papillae in the lymphatics and in round dense intracellular conglomerations in the cells which are known as globi Globi often contain more bacillary granula than rods and may become large enough to be macroscopically visible The intracellular bacilli are mostly found in the lepra cells which are large polynuclear cells with a foamy protoplasm The lepra cells stem from histiocytes and as such they are part of the reticuloendothelial system Their protoplasm is rich in lipids Before the leproma invades the epidermis it stays for a certain period separated from it by a characteristic leprosy free layer of tissue a phenomenon which A Neisser had observed

Neural leprosy is characterized by interstitial neuritis Absence of granuloma formation is striking The histology of *tuberculoid leprosy* resembles that of Boeck s sarcoid The lesions consist of sharply bordered perivascular granulomas sometimes with a necrotic caseating center Plasma cells are scarce epithelioid cells abundant Giant cells of the Langhans type complete the tuberculoid picture Frazier [953] says that the most typical tubercles of the skin are found not in tuberculosis but in leprosy

The invasion of the nerves may be metastatic and hematogenous or contiguous from the skin The latter is very common and explains the predominance of very peripheral neural changes in sensory nerves over motor paralyses

Tests and Diagnosis —Allergic and serologic reactions have not become as important in the diagnosis of leprosy as in other diseases In advanced cases the Wassermann and Kahn reactions are often positive While many

believe that these are nonspecific reactions some more recent investigators (Gundersen Ole Berner after Fellner[959 960]) believe that a positive Wassermann in a leper means syphilis

Rubino s[965] *reaction* based on the sedimentation and agglutination of prepared mutton erythrocytes with the test serum is negative in nonlepers[966 969] often positive in lepers especially in the tuberous form

Some lepers react to *tuberculin* probably without being tuberculous The serum of nontuberculous lepers may give a positive complement fixation test for tuberculosis These occasional difficulties are further increased by the frequent tuberculous infection of advanced lepers[945 969] (Babes after J Jadassohn[945])

The serum of lepers is highly toxic to growing young *plants*[970] in contrast to the serum of patients with syphilis or tuberculosis

Allergic skin reactions with allergens derived from *lepromas* have become important[971 97] Silent immunization in leprous surroundings and anergy must be considered in the interpretation

The *Mitsuda*[971] reaction is not so much used to establish the diagnosis of leprosy as to test the immune biologic defense of a patient in order to gain a basis for prognosis The test consists of the intracutaneous injection of 0 1 c c of lepromin an extract from lepromas[961] If the reaction is positive a papule develops in the second week It reaches its acme in the fourth week with a nodule ½ — 1 cm in diameter which eventually may ulcerate and slowly heal The papule has a tuberculoid structure The test is often positive in healthy persons from leprous surroundings and in tuberculoid leprosy it is often negative in lepromatous leprosy and doubtful in cases with histologically nonspecific inflammatory lesions The negative lepromin reaction in lepromatous lepra with abundant bacilli is explained by a lack of defense to the infection and is therefore considered a bad prognostic sign The positive reaction is considered as an indication of vigorous defense and relatively favorable prognosis (see tuberculoid leprosy and law of Jadassohn and Lewandowski pp 180 and 242)

Febrile and focal reactions to 0 2 to 3 0 grams of *potassium iodide* or to intravenous injections of sodium iodide occur frequently in lepers and have diagnostic value The serologic reactions may become activated and the increased nasal secretion may lead to the detection of leprosy bacilli in smears

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[965] Rubino M C Séro-diagnostic de la lèpre par l agglutino-sédimentation des globules rouges de mouton formolés Bull Acad de méd Paris 105 890-893 1931 also Ann Inst Pasteur 47 147 172 1931

[966] Lépine J Markianos and Papayoannou A Valeur pratique de la réaction de Rubino pour le séro-diagnostic de la lèpre Bull Soc path exot 25 543 193 Zbl 43 40?

[967] Hombria M Zum serologischen Studium der Lepra Actas dermo-sif 25 193 200 193? Zbl 44 638

[968] Montanes P Diagnostischer Wert der Rubino schen Reaktion bei Lepra Actas dermo-sif 24 241 262 193 Zbl 41 550

[969] Brant J Erythrocyten-Senkungsreaktion bei Lepra Latv arstu Zurn 11 619-6 3 1932 Zbl 44 33 1933

[970] Macht D J Phytopharmacological Studies on the Sera of Pemphigus Syphilis and Leprosy Acta dermat Kyoto 18 1?6-137 193

[971] Mitsuda K Troisième conférence Internationale de la lèpre Communications et Débats Paris 193? J B Baillière et fils

[972] Bargehr P Spezifische Hautreaktion bei Lepra Ztschr f Immunitätsforsch u exper Therap 47 529-531 19?6

which were previously negative. *Biopsy* of the skin or nasal mucosa, testing of the serum of blisters produced by carbon dioxide snow, and puncture of lymphatic nodes are some of the laboratory methods successfully used to find bacilli. For the preparation of *nasal smears* the mucosa should be gently scraped without causing bleeding.

Clinical similarity to a great number of dermatoses may develop in one or the other stages of this chronic disease. Psoriasis, ichthyosis, mycosis fungoides, leukemia, blastomycosis, syphilis, lupus erythematosus, vitiligo, and a number of other skin diseases may occasionally be suggested by atypical leprosy.

The course, the occurrence of leprosy in the surrounding region, macules and lepromas, biopsy, and above all anesthesia will usually decide the question. If the cooperation of the patient in testing of the sensory functions is lacking, *the histamine test* may prove valuable. The skin is pricked with a needle through a drop of histamine salt solution 1 — 1000. In paralysis of the sensitive nerve endings a wheal appears as in the normal skin but it lacks the red areola which is normally seen. This is called a negative histamine test. Pardo Castello and Tiant[961] found this test negative in the cutaneous lesions of leprosy. The most difficult problems, however, may arise from nervous diseases, and particularly from syringomyelia. Here the anesthesia is more sharply bordered, and the muscular atrophy (which in leprosy is usually restricted to the anesthetic parts of the hands) affects the arms and shoulders. Scoliosis, bulbar symptoms, pathological fractures of the long bones, ataxia, central unilateral facial paralysis, tremor, spasms—in short, central neurologic symptoms and signs—are more suggestive of syringomyelia. The neural phenomena of leprosy are usually of peripheral character.

Treatment.—No specific therapy is known. The derivatives of the chaulmoogra oils which are obtained from several tropical trees are so far the most effective drugs. Recently promin, a sulfone derivative, has given encouraging results.[973]

[973] Faget, G. H., Pogge, R. C., Johansen, F. A., Dinan, J. F., Prejean, B. M., and Eccles, C. G.: Promin Treatment of Leprosy, Pub. Health Rep. 58: 1729-1741, 1943.

CHAPTER XIII

DERMADROMES OF INTOXICATIONS

A poison may cause a dermatosis by external contact without systemic interference (discolorations by dyes necroses by caustics) or by damaging the skin as part of the damage to the entire system In the latter case one must separate the intoxications in the strict sense from the allergic reactions In *intoxications* the causative agent is toxic to all individuals if it is absorbed in a certain dose the damage it produces depends on the nature the amount and concentration of the poison and also on the length of time it acts excessive doses being lethal The poison can be excreted and antidotes may reverse the process There is no incubation period and the agent may be found in the tissues by chemical analysis These are some of the features characterizing intoxication in contrast to allergy (Tzanck after R L Mayer[974])

Thallium alopecia and argyria are examples of this sometimes called classical type of toxidermia

In the case of *allergic reactions* a specific alteration in the capacity to react acquired by previous exposure to the agent [975] is the dominant pathogenetic factor though the nature and dose of the poison (allergen) should not be underrated The allergic dermatoses have been the subject of several recent monographs[9 5 976] and their character as a manifestation of internal disorders is not yet clearly enough understood to warrant more than a short mention in this book The dermatoses caused by metabolic and bacterial toxins are being dealt with in other chapters Thus only the *skin manifestations of systemic poisonings* in the strict sense of the term shall be discussed in the following chapter

Arsenicals

Arsenical poisoning occurs in a great variety of circumstances It is an industrial hazard in the mining and smelting of many ores especially gold and copper The gases from the copper furnaces the commercial metal sulfides as well as sulfuric acid are often contaminated with arsenic Lead arsenite calcium arsenite and Paris green are rat poisons and agricultural insecticides used on such important crops as cotton tobacco apples grapes and vegetables[977] Several arsenites sulfides of arsenic and other compounds are bright colored pigments which in spite of modern paints and legislation have been and probably still are in occasional use in wall paints wall papers toys and colored papers

Medical administration of arsenicals is a common cause of arsenicism Suicidal and homicidal attempts and laboratory and industrial accidents are

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[974] Mayer R L Toxicodermien Handb d Haut u Gk 4 2 1 252 1933

[975] Sulzberger M B Dermatologic Allergy Springfield Ill 1940 Charles C Thomas

[976] Urbach E Allergy New York 1944 Grune & Stratten

[977] Ayres S Jr and Anderson N P Cutaneous Manifestation of Arsenic Poisoning Arch Dermat & Syph 30 33-43 1934

relatively rare by comparison. Mass poisonings affecting many thousands of people and remaining unexplained for a long time have occurred in a great number of instances. Such a so called epidemic terrified Paris in the 1830's. About 40 000 persons became victims of a disease then called acrodynia which later was identified as arsenic poisoning. In later epidemics the cause was established by means of modern chemistry. There were several mass poisonings by wine from vineyards where arsenicals had been used for spraying. The last one occurred on ocean liners in 1932.[978,979]

In 1900 sulfuric acid containing arsenic used in converting cane sugar into invert sugar for beer brewing in England caused one of the greatest mass poisonings in history. Drinking water contains arsenic in toxic amounts (more than 0.2 mg per 1000 c c) in many localities (Kathe after R. L. Mayer[974]). Chronic skin manifestations are likely to be found among the inhabitants as was shown in the description of the drinking water epidemic in the little Silesian mining town of Reichenstein.

The descriptions of these epidemics (partly given by such masters of dermatology as Vidal, Barthélemy and A. Neisser and their schools) laid the foundations of our present knowledge of arsenical intoxication which is one of the best studied of all human poisonings.

Acute arsenical poisoning is characterized by severe gastrointestinal symptoms which resemble cholera and may cause death in a short time often after a few hours. Excessive lacrimation and salivation are early manifestations.

Within a few days or a week polyneuritis with multiple paralyses may develop together with cutaneous symptoms and may last a long time. Formication, pruritus, numbness, wrist drop and tabes like syndromes are characteristic neurologic symptoms. There exist a great variety of clinical pictures, e.g. psychoses and agranulocytosis, but nervous and cutaneous symptoms are significant if not the dominating features of the subacute and chronic cases.

The *diagnosis* of arsenic poisoning[977] depends on the history, clinical appearance and the presence of arsenic in the urine or hair in an amount which is decidedly above or a multiple of the value which may occur under normal conditions. Geographic location, drinking water peculiarities of the soil or a diet rich in seafood which may contain as much as 8 mg per kilogram are factors which must be considered. Representative normal figures have been stated as 9.7 mg per hundred grams substance for the hair and skin, 17.2 mg for the nails and 10.4 mg for the urine.[980] Wilcox[981] and Ayres and Anderson[977] recommend the Guthzeit test for urinary analysis which is a relatively simple color test.[982]

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[978] Thorel and Vi zent A propos d un intoxi ation coll ective par l ars i Ann d d rm t et syph 3 618-6 i 103

[979] Mühl I Ueber i Masse ergiftu g na h Weing nuss an Bor l D tsch med Wchnschr 193? I 8-4-8 5

[980] Bill t r O an l Marfurt F De la t ur no male en arse ic dans l corps humain H lvet chim acta 6 80- 84 19-3

[981] Wilco W Acut Ars ni al Poisoni g Tr Med Leg Soc Lo I 23 148-16? 1930

[982] Aut l th W D tection f Poiso ed 4 Philad lphia 1915 P Blaki ton s Son & Co

Sometimes it is possible to demonstrate arsenic in the biopsy specimen of skin lesions [983, 984] A progressive diminution of arsenic in the urine with clinical improvement under sodium thiosulfate therapy and the recurrence of symptoms on exposure to arsenic would be further proof A positive patch test would show that there has been enough exposure to arsenic to produce sensitization

Dermadromes —The earliest skin manifestation of arsenical poisoning is *pruritus* which in some cases is restricted to the palms and soles Conjunctivitis coryza and *puffiness of the eyelids* are also early warning signals which are observed more often in the course of prolonged arsenical treatment than after acute poisonings with one large dose Other frequent and early symptoms are dis



Fig 144 —Exfoliati e d rmatitis (erythro lerma) following ars nic poisoni g (Courtesy Dr Ca r tt Coop)

tinctly bordered *palmar and plantar erythemas* Their diagnostic importance is great because of the ease with which they can be noticed in ambulatory patients under continual arsenic treatment The accumulation in the sweat glands which concentrate and eliminate the arsenic (Hutchinson after Ullman[985]) as well as the arsenophile keratotic epidermis are responsible for the site of the erythemas *Palmar plantar sweating* is known as an early symptom [986]

[983] Osborne E D Mi roc mical Studies of Arseni in Ars l D matiti Ar h D mat & Syph **15** 37 19?

[984] Osborn E D Microch mical Studies of Ars nic in Ars ni al Pigm ntations a d K erat ses Arch Dermat & Syph **12** 773 788 19

[985] Ullman K U ber Arsen a th m im Bild akut r wi chroni ch r Arsenv rgiftu g n Klin Wchnschr 1931 II 1 05-1 08 1544 1549 1931

[986] Simon R D G I Skin Manif statio s in Ars nic Poiso ing N d rl tijd hr v G k pp 5367 5368 193 Zbl **53** 19

Widespread or even truly generalized *rashes* following the intake of arsenicals may be seen together with or following the palmar plantar erythemas

Scarlatiniform morbilliform and *erysipeloid* erythemas are also known Of greatest importance are the *eczematoid eruptions* which if further intake of arsen icals is not halted may rapidly develop into generalized exfoliative dermatitis which is such a great hazard in the use of the arsphenamines (see there) while it is rarely provoked by the inorganic arsenicals

Generalized rashes may also be urticarial vesicular or bullous K Ull mann[987] emphasizes the sequence of pruritu urticaria and edema followed by circumscribed and later generalized erythemas

The generalized exanthems may also appear as large or small scaly patches in some instances *resembling pityriasis rosea* or *parapsoriasis* Older lesions of this kind may have a heavier covering with scales and thus imitate *psoriasis* closely The arsenical erythema may also surround and accentuate pre existing psoriatic lesions [974]

The eruptions sometimes *imitate lichen planus* This is a remarkable fact with regard to the great efficacy of ar enic in lichen planus No generally accepted explanation for this clinical coincidence has been offered and cannot be expected before more about the etiology of lichen planus is known

Scleroderma as a probable ar enical equel [9 4 988 989] has been observed in a considerable number of instances Generalized *poikiloderma* as a permanent damage after ar enical dermatitis is also on the long list of rare arsenical arsphen amine reactions [990] Recently nine ca es of *acrodermatitis chronica* atrophicans have been observed in a group of wine growers affected with occupational ar senicism [991]

Edema is a common symptom in ar enical eruptions There may be only slight puffiness of the eyelids and cheeks but generalized edema is hardly ever absent in the severe forms of dermatitis

Petechiae and other *hemorrhagic* symptoms are of rather grave prognostic significance [95] *Herpes oster* is reported to occur in 1 8 [99] 8[986] or even 10 to 20 per cent[993] of the ca es The high incidence of herpes zoster in the English beer epidemic was one of the facts which pointed to arsenic as the causative factor

Pustules ulcers necroses and perforations of the *nasal septum* are caused by the local external caustic effect of the ar enic

The *oral mucosa* may participate early in the toxic syndrome with pharyn gitis and gingivitis Ulcerative stomatitis or glossitis may occur in severe cases

[987] Ullma I Ars nkeratos un l Ar nwarzenbildung Zbl **35** 344 1931

[988] Ayres S Jr Scleroderma a Possible Manifestation of Ch onic Arsenic Poisoning Arch D rmat & Syph **2** 4 1920

[989] Ayres S Jr A Fifth Cas of S leroderma With Ars ic in the Uri e Arch D rmat & Syph **3** 45- 47 19 1

[990] Ca on A B I a litz Ka y M B a I Fischer J I Poikilodermatik Changes in Skin Following Arsph ami D rmatiti J A M A **118** 1 1?9 1942

[991] Hen kma n H A rod matis hro i a atrophi an bei Winz rn mit Ars schädigungen Arch f D mat u yph **179** 6 0 193

[992] N L H pes ost während A B h ll ng Monat h f prakt D rmat **21** 30? 1890

[993] Cey r L Ü r Haut & I ru g n beim Arseni ismus und Betrachtungen über die Massen rkranku g n i B f h t in in S hlesi n Arch f D mat u Syph **43** 2 1 1898

The *hair* is almost always diffusely shed. The alopecia is complete in severe cases of arsenical dermatitis.

The *nails* usually record severe dermatitis as well as acute, especially single dose, poisonings by cross furrows (Beau's lines) or with white[553] or gray cross lines. The latter have become known as Mees' bands[994, 996] and are often associated with polyneuritis arsenicosa. They are dull glistening bands extending across the breadth of each finger nail. The bands appear at the lunula about eight weeks after the poisoning. If one adds 10 days for every 1.1 — 1.2 mm of the distance from the proximal border of the lunula to the distal border of a band one can determine the approximate date of the poisoning. The arsenic content of a band has been found to be 10 times higher than in the undiscolored parts of the nails.[996]

The condition is apparently identical or similar to the *leukonychia striata* which was observed in many instances during the English beer epidemic and in other instances of arsenical poisoning. The nails may be shed after severe arsenical dermatitis.

Arsenical dermatitis of all types heals with *hyperpigmentation* of varying intensity which may even develop without preceding noticeable inflammation.

The distribution, depth and duration of the hyperpigmentation vary within wide limits. The areas which have a natural tendency to darken, such as the genitals, groins, umbilicus and mammillae, as well as scars, healing skin lesions and pressure and friction points are often highly pigmented.[986]

The individual tendency to pigment has a much greater influence on the melanosis than the size of the doses of arsenic. Melanosis may appear as early as 12 days after the onset of arsenical medication and after small doses. On the other hand, severe poisoning may fail to produce it. This is well demonstrated by the fact that in poisoning from drinking water with generally equal supply *to the population only some persons develop marked melanosis.* The discoloration may start insidiously and reach any, even the severest, degree.[997]

The diffuse type of arsenical melanosis is so similar to the appearance of Addison's disease that during the great beer epidemic in England most cases were so diagnosed until the autopsies failed to reveal adrenal changes. The covered parts of *the skin seem to darken more than the open ones*,[974] *although* the face is frequently affected. In a minority of the cases a dense, regularly reticulated or dappled pattern of pigmentation and depigmentation may cover wide areas, especially the back. This type of arsenical melanosis has been called "*raindrop pigmentation*" because of its resemblance to a window pane covered *with raindrops*. *This characteristic type of arsenical pigmentation is often found* in chronic arsenicism due to drinking water or prolonged administration of inorganic arsenicals.

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[994] Mees, R. A.: Een verschijnsel bij polyneuritis arsenicosa, Nederl. tijdschr. v. geneesk. 1919 I: 391-396.

[995] Bark, L. F.: Exfoliative Dermatitis in Accidental As Poisoning; Mees Band, Urol. & Cutan. Rev. 46: 567-597, 1942.

[996] Wigand, R.: Das Meessche Nagelband bei Polyneuritis arsenicosa, Münch. med. Wchnschr. 87: 832-834, 1940.

[997] Thron, B.: Arsenical Pigmentation, Arch. Dermat. & Syph. 24: 479, 1931.



Fig 145 Arsenical m lanosis rai lrop app arance (Courtesy Divi ion of Dermatology D part m t of Medicine Uni rsity of Chicago)



Fig 146 —A se i al m l osi rain lrop appeara e

Arsenical melanosis has also been seen to follow the pattern of underlying large veins [978]

The *depigmenting* tendency after arsenical dermatitis is best observed in Negroes [998]

In rare instances the *oral mucosa* participates in the pigmentation, although the lack of oral pigmentation has often been emphasized as a differential criterion against Addison s disease The arsenical melanosis may vanish rapidly with the other symptoms of the intoxication but more often it persists much longer or even permanently

The arsenical pigment is *melanin*[999] and as such is iron free It can be distinguished from arsenic crystals[984] which lie mostly between the cells



Fig 147 —Arsenical keratosis of palm after indiscriminate use of Fowler s solution in psoriasis

Keratoses are the most common and characteristic and the most easily detectable of all skin manifestations of chronic arsenic poisoning

The keratoses may appear within a few weeks after the start of arsenic intake or as late as many years after the medication or other exposure has been stopped [1000] An erythema may or may not precede their appearance

The characteristic sites of the hyperkeratoses are the palms and soles with *their peculiar affinity for arsenic* The areas of friction and pressure which normally tend to callus formation are especially apt to develop arsenical hyper

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[998]Cannon A B and Karelitz M B Vitiligo From Arsphenamin Dermatitis and From Arsenic Arch Dermat & Syph 28 642-651 1933

[999]Can O Histologie d r Ars m la o e B itr z path Anat u z allg Path 60 2-38 1915

[1000]Montgomery H Arsenic as an Etiologic Agent in Certain Types of Epithelioma Arch Dermat & Syph 32 18 236 1935

keratoses Thus the plantar arch and the center of the palms remain relatively free from circumscript lesions but they are not immune against diffuse keratosis Occasionally circumscribed keratoses may appear on the back on the chest on the extensor surfaces of the elbows and knees on the heels or on the dorsa of the hands and feet [1000 1001]

Hyperkeratoses may be diffuse and cover the entire palms and soles Much more characteristic however are the circumscribed lesions They are often called warts but they are less circumscribed and vascular than ordinary warts They are cornlike accumulations of horny tissue and because of their completely epidermal structure they are more transparent than warts or corns Their color is usually pale yellow but thicker layers may take on a dirty gray or even slate or brown hue The opening of a sweat gland is sometimes visible at the top of a small lesion The size varies from that of a millet seed to a pea or even an almond *Hyperidrosis* is a frequent annoying accompaniment which may even be the presenting symptom in cases of arsenical keratosis



Fig 148 —Tra ition of arse i al kerato is into a er

There exists only a very rough parallel between the appearance of the keratoses and the dose and length of time of arsenical exposure Examples of extensive keratoses after small amount of arsenic and complete lack of keratoses after huge doses are well known [1000]

Chronic intoxication with inorganic arsenicals is especially apt to cause keratoses while they are rarely seen among the tremendous numbers of people treated with arsphenamines The circumscribed keratoses usually disappear

[1001] Kum r L Mächtig papill mat se Wu h u g n uf ekz matöser Haut Z I 18 840 19 6

PLATE II

1 Lupus erythematosus acutus. Rapidly fatal case

2 Arsenical keratosis with carcinoma

3 Leaking aneurysm of the abdominal aorta. Giant ecchymose

4 Hypertension. Chronic nephritis. Pruriginous eruption

5 Vagabond's skin

6 Erythema palmare. Mitral insufficiency





3





5





Plate II

gradually with the elimination of the arsenic Sometimes however they are permanent If they are removed they grow back rapidly Such keratoses of many years standing are *precancerous* lesions

Montgomery[1000] saw *epitheliomas* develop in 20 per cent of his 85 cases of arsenical keratosis but the percentage is likely to be smaller in less preselected material than is encountered at the Mayo Clinic

The cancers are usually of the squamous cell type Some assume features of Bowen's disease by the formation of grouped or circinate lenticular, crusty or scaly papules But it has not been sufficiently proved that Bowen's disease and superficial epitheliomatosis generally are due to arsenic as had been suggested[1002] Arsenical epitheliomas may also appear independently of keratoses They may occasionally look like superficial epitheliomatosis forming thin scaly plaques which however often lack the thin threadlike pearly border of this variety of skin cancer[1000]



Fig 149 — Arsenical keratosis resembling Bowen's disease

Basal cell epithelioma is very rare The degree of malignancy is relatively low metastases occurring very late Arsenical cancers of the urethra, bladder and bronchi have been observed in rare instances[1003]

The cancers are not very malignant They metastasize late and are seldom and only after a long time destructive They respond well to radiation and even the excision of relatively large cancers may be successful In all cases of

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[1002] Anderson N P Bowen Precancerous Dermatosis Benign Superficial Epitheliomas Arch Dermat & Syph 26 10 103

[1003] Goeckerman W H and Wilhelm L F X Arsenic as Cause of Cancer of Mucous Membranes Arch Dermat & Syph 42 641-648 1940



Fig 150 — Large arsenical cancer over Achilles tendon Indiscriminate use of Fowler's solution against psoriasis



Fig 151 Superficial epitheliomatosis in a patient with arsenical keratoses and a history of indiscriminate use of Fowler's solution

multiple epitheliomas of the skin the possibility of an arsenical etiology should be considered[1000,1001]

Arsenical keratoses should be *treated* by any superficially destructive measure such as dry ice fulguration etc The use of keratolytic salves gives only temporary results The value of sodium thiosulfate medication either by the intravenous injection of 1 gram daily or by mouth is controversial

Arsenical epitheliomas should be treated like other skin cancers

Arsphenamines—The dermatoses due to the use of arsphenamines are either arsenical in character or they are specific allergic phenomena[1004]

The *angioneurotic syndrome* or nitritoid reaction occurs immediately after an intravenous injection of any one of the arsphenamines, particularly if the injection has been given at a fast rate

Itching may be the first symptom of this reaction but it is quickly followed by a feeling of great congestion and pressure in the head dyspnea palpitation and anxiety There is acute redness of the face as if the patient had inhaled amyl nitrite The face may become acutely swollen Soon the bright erythema becomes cyanotic and in severe cases the patient may become unconscious and the breathing stertorous The terrifying episode is usually over after a few minutes especially if adrenalin is injected Death has rarely occurred An exceedingly slow rate of injection change of the type of arsphenamine and lowering of the dose are the best means of *prevention*

Urticarial or in rare instances bullous rashes appearing in the same site immediately or shortly after the injection are called *fixed* arsphenamine eruptions

The severest cutaneous disease following the administration of any one member of the arsphenamine group is *generalized exfoliative dermatitis* This dangerous dermadrome usually starts after several injections have been given or not infrequently a few weeks after the series of injections has been finished

Fever anorexia and slight erythema often precede the main rash which appears first on the extensor aspects of the knees and elbows as a morbilliform or scarlatiniform eruption Within a week it develops into generalized acute erythroderma There is usually widespread or even generalized weeping edema fever albuminuria and hepatitis Septic symptoms especially multiple boils and foci of cellulitis and necrosis are a prominent feature This may last for many weeks Gradually the skin dries up and is exfoliated in large sheets especially about the hands and feet Melanosis of moderate degree follows frequently There is always diffuse effluvium of the hair and often the entire hair falls out The nails may also be shed The prognosis is most dubious Death from sepsis occurs frequently

A large recent American series gives the incidence of severe crustaceous dermatitis as 0 7 per 1000 injections The patients were not previously treated with arsphenamine[1005] This seems much higher than other observations

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[1004] Birnbaum G Salvarsanschädigung n der Haut Zbl 49 0 106 1936

[1005] Waugh J R and Milovich F Severe Reactions to Arsphenamine Among 30,0 Patients Previously Untreated Ven Dis Inform 21 359-394 1940

Allergy to arsphenamines in cases of dermatitis has often been demonstrated by positive patch tests[1006] Women were twice as often affected as men[1005]

The *treatment* requires daily injections of 1 gram of sodium thiosulfate and best nursing care Penicillin is probably helpful in combating pyogenic infection Liver extract has often been recommended

Convalescents should not be subjected to any further arsenical treatment

Early acute arsenical erythema or *erythema of the ninth day* is a febrile multiform rash of unknown etiology occurring in about 3 per cent of the patients treated for the first time with trivalent arsenicals[1007] The rash is described as generalized and composed of irregularly macular or morbilliform lesions clearing up after 2 days Arsenical treatment may be continued with extreme caution only but is better replaced by penicillin[1008]

Other rare eruptions following the use of arsphenamines include *lichen planus* and *lichen spinulosus*[1009] *Jaundice* is a frequent after effect of arsphenamine treatment There is no consensus whether arsphenamine alone allergy syphilis another infection or a combination of factors are responsible for the frequent cases of hepatic disease in the course of antisyphilitic treatment with neoarsphenamine[1010]

Gold

Gold poisoning is almost exclusively due to medication gold sodium thiosulfate (sanocrysin) being the most widely used compound The general symptoms follow the pattern of other heavy metal intoxications including arsenic There may be nephritis enteritis hepatitis and a depression of the hematopoietic system in severe cases ending in agranulocytosis or aplastic anemia

Ill effects mostly of a mild nature were estimated to occur in about 10 per cent of 1400 tuberculous patients treated with gold compounds[1011] They were much more common in the early days of gold therapy when high doses were advocated

Dermadromes —The skin is most often affected[1012] The injection of a gold salt even in small quantity may cause immediate or early *nitritoid reactions* with a flushed face and a sensation of giddiness sometimes with severe cervical pain Such reactions occurred most frequently after sodium thiomalate (myochrysin)[1013 1014] They are very rare after gold sodium thiosulfate if it is injected slowly into the vein

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[1006] Schoch A G The Patch Test and the Element of Syringe Contamination in Arsphenamine Sensitization Dermatitis J A M A 98 1367 193

[1007] Cañizares O and Thomas E W Early Acute Arsenical Erythema Arch Dermat u Syph 39 567 1939

[1008] Leifer W Danger of Continued Arsenotherapy in Cases of Erythema of Ninth Day Am J M Sc 210 458 1945

[1009] Volavsek W Seltene Salvarsanschäde Dermat Wchnschr 114 409 120 1942

[1010] Winkler M Dermatitis and Icterus Following Arsphenamine and Bismuth Therapy of Syphilis Dermatologica 81 297 309 1940

[1011] Mayer O Gold Treatment of Pulmonary Tuberculosis Brit J Tuberc 28 131 139 1934

[1012] Fellner M Die Goldtherapie in der Dermato-Venerologie 71 43 33 1932

[1013] Lintz R M Toxic Reactions With Gold Salts in Treatment of Rheumatoid Arthritis J Lab & Clin Med 26 1629-1634 1941

[1014] Nicolas J Lebeuf F and Mollard H Sur quelques accidents insolites de la chrysothérapie (une crise nitritoide) et de nouvelles localisations tuberculeuses Bull Soc franç de dermat et syph 39 874 876 1932

All the familiar types of toxic exanthems have been observed Morbilliform and scarlatiniform rashes are relatively common multiform and bullous eruptions are rare

Some exanthems resemble pityriasis rosea but they lack the primary lesion [1015] Itching may be the first symptom of all these rashes and should be reason to discontinue the treatment



Fig 15 Acut ... e zematoid eruption p ovoked by gold therapy of ch o i lupus e yth matosus

Hemorrhagic eruptions seem to occur more frequently than in arsenical poisoning [9 4 1016] The tuberculosis or syphilis of the patients treated with gold may have some importance in the pathogenesis of the purpuric [1017] mostly petechial rashes These eruptions are frequently accompanied by other hemorrhagic phenomena especially hematuria Naturally all hemorrhagic manifestations are potentially serious *Generalized exfoliative dermatitis* with loss of hair and nails though rarely with a fatal outcome [1018] has been observed [101 1019]

Lichen planus like eruptions seem to be a feature of the gold dermatoses [1020] They may be subacute with violent itching vesicles and blisters or even turn into generalized exfoliative dermatitis More commonly they consist of relatively

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[1] Wil I J and Courvill C J Pityriasis-Rosea Lik D rmatitis Followi g Th rapy With Myochrysin Arch D rm & Syph 42 1105 111 1940

[1] Emile-Weil and Bouss r J Les f t ts hém rh giques po t-au iques Sa g 6 825 839 193

[1 7] Coug rot H and Blum P Syn lrom hémor hagi que d clan hé tardi m nt par l or Bull Soc franç d d rmat et syph 40 877 878 1933

Mart nst in H Di B h dlung l s Lupus erythematod mit Krysolgan Klin Wchnsch 1 35-923 1922

[1] B Unf nt A J C Ony hla an l Al pecia Aft r Gol l Derm titi Ned l tijdschr v Geneesk pp 2613 614 193 Zbl 58 00

[1020] Mill G L Lich n Planu Du to G ld Th rapy Bull Soc franç de d rmat et yph 46 384 1939

large flat papules which have a tendency to coalesce into large plaques of the lichen corneus type [1021]

There are two kinds of skin *discoloration* known to follow the administration of gold One is caused by deposits of *melanin* in the upper cutis This type corresponds to the more common arsenical melanosis and is reversible It frequently develops after gold rashes [1022] but it may also be primary and occur after small doses [1023]

The second type is of greater and more practical interest The injected salt is reduced to *metallic gold* and deposited in the lower cutis in the subcutis in the kidneys and in all parts of the reticulo endothelial system

The visible discoloration is restricted to the skin exposed to light No difference in the gold content between discolored and apparently normal skin can be found by means of spectroscopic or histologic analysis [1024] With the slit lamp gold particles can be demonstrated in the cornea

The darkening is diffuse and slate to graphite gray in color Most observers emphasize a bluish or purplish hue [1025] The dyschromia seems to be permanent Lorenzen[1026] found that none of his tuberculous patients who had received more than a total of 0 15 Gm of sodium aurothiosulfate per kg body weight escaped chrysiasis but none of those with a total of less than 0 05 Gm per kg developed it The trouble becomes visible one to three years after the treatment Mild cases of *chrysiasis* as this discoloration caused by gold deposits is called do not as a rule constitute a very conspicuous disfigurement

With the commonly used doses of up to 50 mg per injection the danger of producing chrysiasis is remote

Hyperkeratoses and diffuse keratoderma after gold treatment are very rare [1023, 1027]

Oral symptoms of gold eruptions have frequently been described Dryness and metallic taste are often the first symptoms of gold intolerance Simple erythematous or vesicular stomatitis may occur with edema and ulceration of the tongue in severe cases Gold stomatitis has been seen to precede rashes [1028] Clinically and histologically typical oral lichen planus almost always without accompanying cutaneous lichen planus has been noticed relatively often [974, 1029, 1030] as a sequel of gold intolerance The lesions are white irregular thin or slightly

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[1021] Cougerot Vial and Nekam Lichen ou prurigo verruqueux intense et très étendu Bull Soc franç d d mat et syph 43 1592 1 85 1936

[1022] Sézary A Horowitz A and Soullard J Pigmentation en nappes et acné cornée consécutives à une érythrod mi au iqu Bull Soc fran de dermat et syph 40 1616 1619 1033

[1023] Irgang S Keratod rma and M lanod rma Accompanying Therapy With a Gold Compound Arch D rmat & Syph 34 6 4-623 1936

[1024] Koch A G Ch y iasis Arch f D rmat u Syph 178 323 330 1938

[1025] Schmidt O E I Ch y iasis Arch D rmat & Syph 44 446-4 2 1941

[1026] Lorenz J N Ueber das A ft ten von Chrysiasi b i früh r mit Nat iumaurothio ulfat behand lt Lung ntuberkulösen B itr z Klin I Tub rk 76 656-636 1931

[1027] Roxburgh A C Iag A I M a d Gordo D *Gold D rmatitis With Hyp rkerato is Brit J D rmat 48* 137 142 1936

[1028] Fourni r L a d Boltan ki F Gold Dermatiti Rev de stomatol 28 681-686 19 6 Zbl 23 679

[1029] Finn rud C W Lupus érythematodes d r Mu dschl imhaut Arch f D rmat u Syph 148 318-3 19

[1030] Mohrmann B H U Li h n planus der Mu 1 chl imhaut nach Goldi han llung D rmat Wchnschr 99 1373 13 6 1934

papular keratoses of the buccal and labial mucosae[1031] They may disappear after discontinuation of the gold treatment

A peculiarity of gold is its activating effect on chronic inflammations and infections especially tuberculous foci The appearance of papulonecrotic tuberculosis under gold treatment has been reported (Medina after Throne et al[1032])

Silver

While there is little known about acute toxidermia caused by silver this metal is more likely to cause permanent deposits and discolorations than any other metal The *dyschromia* from silver is called *argyria* argyriasis or argyriasis

Occupational argyria has been seen in the chemical industry and among workers who blow a silver nitrate solution into glass beads or Christmas tree decorations to silver the inner surface After many years in this trade such craftsmen sometimes become deep black with a metallic sheen[1033 1034] Of much greater importance though rarely reaching the same degree of discoloration is the argyria caused by the use of silver compounds in medical therapy

Silver nitrate pills for peptic ulcer tabes or epilepsy have gone out of fashion but the prolonged use of silver nitrate mild silver protein or colloidal silver in nose drops[1035] oral sprays or paints and in genitourinary douches or instillations have produced a great number of cases of generalized argyria Some cases were observed after injections of silver arsphenamines now obsolete[1036] Gaul and Staud[1037] state that after the injection of a total of 8 Gm of silver arsphenamine argyria becomes clinically apparent

The first darkening of the skin may appear as early as six months or as late as fifteen years after the initial use of the silver drug but two to three years have been found as the average in 68 cases of the Mayo Clinic[1038]

It is remarkable that women outnumbered the males 7 4 in this series

Argyria appears as a slate to bluish gray sometimes bronzed[1039] rarely black diffuse discoloration predominantly of the skin exposed to light[1040] Thus the forehead face neck and the dorsa of the hands are the main sites of the trouble but in severe cases the entire body surface may be involved The conjunctivae may be stippled and the caruncles of the inner canthi the gums and the palate have often been found slate colored

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[1031] Lo tat-Jacob and Legrain P Lupu éryth mateux trait par l or Apparition d un lichen plan buccal int e Bull Soc franç d d mat et yph 38 786 787 1931

[1032] Throne B Kl gsbury J a d Myers C N Unu ual Clinical Manifestation Followi g Intra enou Administration of Gold Compounds Arch D rmat and Syph 25 494 507 193_

[1033] Teleky L Gew bliche Argyrie Zbl f G werb hyg 2 1 8 153 1913

[1034] Harker J M d Hunter D Argy ia Brit J D mat 47 441 1935

[1035] Woodward M R Argyria From the Use of Colloi ial Silver Iodi le I tranasally Am J Dis Chil l 45 1046-1049 1933

[1036] Spiegel L A Discol ration of th Skin an l Mucou Meml r es Resembling Argyria Followi g the U of Bi muth and Silver Arsph namine Arch D mat & Syph 23 66- 86 1931

[1037] Gaul L E and Staud A H Cli ical Spectroscopy Sev nty Cases of C ralized Argyrosis J A M A 104 138 1390 1935

[1038] Hill W R an l Montgomery H Argy ia With Special R fer n e to Cutaneou History Arch D rmat & Syph 44 588 599 1941

[1039] Bei haue Argyria Arch Derm t & Syph 21 706 1930

[1040] Stillians A W Argyria Arch D rmat & Syph 35 67 77 1937

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[1021] Coug rot Vial and N kam *Lichen ou prurigo verruqueux int nse et très étendu* Bull Soc franç de l rmat et syph **43** 1582 1 85 1936

[1022] Sézary A Horowitz A and Soullard J Pigm ntation en nappes et acné cornée co écutives à un érythrodermi aurique Bull Soc franç d d rmat et syph **40** 1616 1619 1933

[1023] Irgang S Kerato l ma an l M lanod ma Accompanying Th rapy With a Gold Compoun l Ar h Dermat & Syph **34** 6 4-629 1936

[1024] Koch A G Chry iasis Arch f Dermat u Syph **178** 3 3-330 1938

[1025] Schmi lt O F I Ch ysiasi Arch D rmat & Syph **44** 446-4 ? 1941

[1026] Lorenz n J N Ueler das Auft t n von Chrysia is bei f üb r mit Natriumau othio ulfat b han l lt n l ung ntuberkulösen B itr Klin d Tuberk **78** 686-696 1931

[1027] Roxburgh A C I age A P M a d Gordon D Gold D rmatitis With Hyperk ratosis Brit J Dermat **48** 13 142 1936

[1028] Fourni r L a d Boltanski E Gol l D rmatitis Rev de stomatol **28** 681 656 19 6 Zbl **23** 6 9

[1029] Finnerud C W Lupus é ythematodes der Mundschl imhaut Arch f Dermat u Syph **148** 318-3 ? 19 5

[1030] Mohrmann B H L Li h n planus der Mun lschl imhaut na h Gol lt handlung Dermat Wchnschr **99** 1373 13 6 1934

of argyria but fails to do so in other metallic discolorations e g that caused by bismuth This method of treatment has not yet found general acceptance mainly because it is quite painful[1041] Argyria is an almost permanent trouble Only occasionally has spontaneous usually incomplete regression been reported

Lead

The skin in lead poisoning is said to be yellow and dry often itchy Erythemas pustular eruptions and petechiae occur[1043] The workers who have symptoms of lead poisoning show an incidence of dermatoses mostly dermatitis which is about three times larger than among the workers in the same industry without symptoms of saturnism The incidence is particularly high in the group with gastrointestinal disturbances *Hematoporphyrinemia* which is common in chronic lead poisoning is a factor in the pathogenesis of these dermatoses[1044 1045] However actual sensitization of the skin to lead is very rare[1046] In rare instances metallic pigmentations have been seen The well known *gum line* is a deposit of black lead sulfide produced by the hydrogen sulfide which develops in the tartar The line is blue black or gray and follows the edge of the gums The removable deposits on the border of the gums may also be discolored

Dystrophy and even loss of the nails from lead is known Pain in the nails may indicate nervous disturbances[1047]

Bismuth

Bismuth may although very rarely cause diffuse blue black *discoloration* of the entire skin which resembles argyria[1048] Circumscribed and in some instances extensive black pigmentations of the lips[1049] vagina[1050] and other mucosal surfaces have been described

These however are rare considering the large number of luetics who have been treated with bismuth without any evidence of such discolorations

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[1041] Frut A C rkt he Schädigung durch Hg Ib und Bi in Oppenheim Rille Ullmann Schädigungen der Haut durch Beruf und gewerbliche Arbeit Vol II Leipzig 1926 Leopold Voss pp 161 167

[1043] Filly a d I G R l of L a l in Certain Dermatoses Sovet vrach hur 43 557 566 1930

[1044] Cugg h im R Bl i kz m S hw iz med Wchnschr 63 277 80 1933

[1045] Fisch th H W a l Meerkamp W Bl i rgiftu g D mat Wch sch 102 54 60 1936

[1046] Schwar L an l Tulipan L O up tional Di a es of the Skin Philad lphia 1939 Lea & Febig r

[1048] Luetl H C Sutto D C McMull n C J and Mu hlberg r G W G n rali ed Discoloration of kin Resembli g Argy ia Follo ing Prol nged Oral U s of Bi muth Case of Bi muthia Arch I t Med 57 1115 1936

[1049] Simo R D Bi muthi mu Ned rl Tijdsch Geneesk pp 74 743 1937 Zbl 56 494

[1050] Wi n K V gin l M lanosis Caused by Bi muth Th rapy an l Carci oma of th Cervix Arch D rmat & Syph 42 23 09 1940

Pruritus, nitritoid crisis,[1051] *urticaria morbilliform scarlatiniform pityriasis rosea like*[1052, 1053] or *lupus erythematosus* resembling[1054] eruptions, acne,[1055] and *exfoliative dermatitis*[1056-1059] have occurred They are rarer generally less severe and they do not have the importance of the corresponding arsenical phenomena [1060]



Fig 151 —Blue lin at gingival margin f om bismuth medi ation

The only common surface sign of bismuth poisoning is the *blue gum line* which corresponds entirely to the blue line of lead The bismuth line can often be observed during antiluetic treatment especially around bad teeth The line disappears several months after the discontinuation of the treatment Severe

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[1051] B rtin E and B eton A C ises nitritoides consécutives aux injections de bi muth Paris méd 2 476-47 193

[1052] deWolf H F Dermatitis Medicamentosa Bismuth Arch Dermat & Syph 28 593 531 1933

[1053] Fox H G nerali ed Pigm ntation a d Dermatitis Followi g Bismuth Therapy Arch Dermat & Syph 35 355 356 1937

[1054] Letg s O and I tges A Accidents cuta ıés non-sign alé encore au cours de trait ment bismuthi ques oléosolubl s (Lésions rythros quam uses à ext nsion centrifuge simulant le lupus érythémateux) Rapp Co gr D rmatologi tes Langue f anç 193 pp 42 44

[1055] Tissi F Su di un raro acci l nte della t rapia bi muti a Ac ie da bismuto Boll sez reg Soc ital Dermat 3 51 3 1935

[1056] Bou l ut Gaté J Racouchot J a l Bon l t Intolé an au bi muth avec hypertherml d rmite généralisé des juamati all umi uri t polyn urit Bull S x franç d d rmat et syph 44 569 57 1937

[1057] Bauma n Bi muth De matit 711 48 2 6 1931

[1058] Nicolas J R uss t J a d Thomass t A Erythrod rmi importante au cours d un traitem nt par l hy l x l l bi muth Bull Soc franç l l rmat et syph 44 517 18 1937

[1059] Roed r r J Erythrod rmi s bi muthi ques hez un syphiliti jue ayant f it une érythrod rmi arsénicale C akä d mat pp 340-343 1931 711 48 456

[1060] Julin berg F Di N benwi ku g n d r Wismutbebandlung Han b d H u Gk 18 44 499 19 5

ulcerative [1061] even fatal [1062] stomatitis or glossitis may also develop but this is much rarer than in mercury poisoning

Mercury

It has almost been forgotten that mercury is able to produce the same types of *rashes* which occur due to arsenic gold bismuth and other metals Urticaria follicular and diffuse erythema morbilliform scarlatiniform and papular rashes and also exfoliative[1063] dermatitis are known However they are less common and also less dangerous than the corresponding arsenical dermatoses Macular rashes resembling erythema infectiosum were established as mercury eruptions due to the administration of calomel and the filling of dental cavities with amalgam [1064] The rashes are often the only symptom of mercury intoxication [1063] Scaling and diffuse or reticular hyperpigmentation may follow the erythroderma [1065]

The most important surface symptom of mercurial poisoning is *stomatitis* Almkvist [1063] who has devoted so much effort to the study of mercury poisoning suggested that H_2S which develops in the decomposition of proteins under the gums and in inaccessible pockets of the oral mucosa forms HgS with the mercury carried by the bloodstream He also found that mercury sulfide is more irritant to the oral mucosa than other metal sulfides The first deposits of HgS are found in the loops of the capillaries of the papillae

The first clinical symptoms are usually salivation metallic taste and a feeling of excessively long or dull teeth Soon the gums start to swell and form pockets between themselves and the teeth in which pus is retained permitting prolonged contact of H_2S with the circulating mercury

The inner lining of these pockets is the first site of superficial necrosis From there the stomatitis which is soon complicated by infection spreads to the open surfaces of the gums where pseudo membranes and ulcers quickly form if the process is not halted by treatment and discontinuation of the mercury In severe cases the entire mouth may become affected the tongue edematous the tonsils ulcerated the teeth loose and even pneumonia and fatal sepsis have in the days of the mercurial therapy of syphilis occasionally occurred [1066]

Treatment consists of cleaning and disinfecting the pockets with thin pointed cotton applicators dipped in strong silver nitrate tincture of iodine or any other strong astringent and disinfectant Naturally the teeth should be kept meticulously clean and another drug should be substituted for the mercury preferably the nonmetal penicillin

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[1061] Matras Stomatitis ulcerosa et necroticans bismutica Zbl 56 441

[1062] Beerman H Fatalities Due to Bismuth in the Treatment of Syphilis Arch Dermat & Syph 26 797 801 1932

[1063] Almkvist J Quecksilberschädigungen Handb d H u Gk 18 178 232 19 8

[1064] J ny F Über Quecksilberexantheme bei Kindern Schweiz med Wchschr 60 942 945 1930

[1065] Gougerot H Blum J Bralez and Archambaud R Pigmentation réticulée tonique après érythrodermie hydrargyrique Arch dermat -syph Hôp St Louis 4 366-3 4 193

[1066] Pinard M Maurel G and T m rson Stomatite mercuriell gangréneus mortelle Bull Soc franç de dermat et syph. 43 1507 1508 1930

Aluminum

Urticaria dermatitis pruritus herpes spider nevi perniones brittleness and longitudinal lines of the nails and paronychia are the skin manifestations of a syndrome which Spira[1067] believes to be caused by chronic aluminum poisoning

Thallium

Thallium is a heavy metal which can produce all the toxic effects of this group Sufficient doses cau e severe pains in the limbs especially in the knees salivation stomatitis gastrointestinal and liver symptoms nephritis cystiti peripheral neuritis and disturbances of the central nervous vegetative and endocrine systems[1068 1070]

Dermadromes —A peculiar affinity for the *hair* causes shedding of the head hair by doses which do not cause other toxic symptoms It is still controversial whether this effect on the hair is due to local damage[1071] or whether it is evidence *of an elective disturbance of the endocrine sympathetic system*[1069]

Thallium acetate has been *for its effect on the hair widely u ed in the treat*ment of tinea of children *

If 6 to 8 mg of thallium acetate per kilogram body weight is given in one dose the hair starts to fall after one week and complete baldne s of the head is reached after nineteen days[107]

The eyebrows especially the mesial portion the eye lashes the lanugo the pubic and axillary hair and in experimental rats the whiskers prove more but *not entirely resistant*[1073] *The epilation of the scalp is occasionally spotty* After 3 to 4 weeks the hair starts to grow again and reaches its old vigor after 2 to 3 months This amazing treatment has however been largely abandoned because of a number of fatal poisonings which have occurred either by over dosage or by administration to adult patients or though very rarely in spite of all precautions[1069] Hypohidrosis is one of the sympathetic effects of thallium Other dermadromes of thallium poisoning are rare They include urticarial erythematous[10 4] macular and lichen planus like exanthems After evere single dose poisonings which have frequently been caused by the ingestion of roden ticides containing thallium salts white transversal nail bands comparable to

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* Th r is n se us that only chil lr n up to 10 y ar houl l l tr ated with thallium The p r kilogram loses which are r lati ly l arml ss l chil lr n prov highly toxic in a lults

[1067] Spira L Th Clini al A pect of Chroni Poisoning by Aluminum an l It All y London 1933 John Bal Son & Dani lsson Ltd

[1068] Karr nberg C I N ben rsch l ung n na h th rap utisch r V rabfolgung v n Thallium Ztl 42 1 31 193 1933

[1069] Buschk A an l P r B Di bi logisch n Wirkung n u l di p akti he B l utung des Thallium Erg b n l allg Path u path Anat 25 1 7 1931

[1070] Buschk A an l P ser B Erg b isse der Thalliumf rs hung u l ihr prakti sch B l utu g Klin Wchnschr 11 124 l 1 51 1289 129 1932

[1071] Truffi C Azione biologica d l ac tato di Tallio A ch d sc bi l 13 271 319 19 9

[1072] C l waky F Erkranku g n d r Haar un l des Haarbod ns Handb l H u Gk 13 1 1 9 468 193

[107] Krel Thalliumv rgiftung Ztl 81 621 193

[1074] Phila l lphy A Hautschädigungen durch Thallium Dermat Wchnschr 98 78 80 1934

Mees's bands in arsenic poisoning have been described [1074,1075] and thallium has been found in the nails.[1076] The local application of salve containing thallium acetate for the purpose of epilation has proved effective but has resulted in a great number of systemic poisonings.

Carbon Monoxide

Carbon monoxide poisoning rarely causes skin manifestations. Shillito, Drinker and Shaughnessy[1077] did not mention any skin damages in their survey of 21,143 cases, but it seems that this report did not pay enough attention to the cutaneous symptoms.

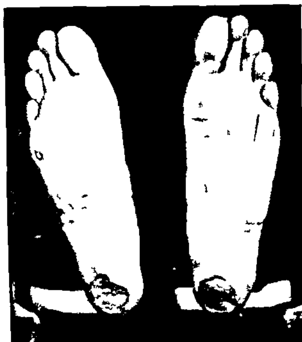


Fig. 155.—Localized gangrene following carbon monoxide poisoning. (From Siffert, E. A.: J. M. Soc. New Jersey.)

The cherry red lips and deep *cyanosis* of persons poisoned with monoxide gas is generally well known. Local *edema* of the extremities was known to the older observers. It may be related to the *circumscribed necroses* found after severe gas poisonings.[1078-1080] The lesions start as serous or hemorrhagic bullae which

[1075] Adler, A.: Nagelveränderung bei Thalliumvergiftung, Derm. Ztschr. 62: 259-261, 1933.
[1076] Wilkens, W.: Fall von akuter Thalliumvergiftung, Zbl. 52: 193, 1935.
[1077] Shillito, F. H., Drinker, C., and Shaughnessy, T. J.: The Problem of Nervous and Mental Sequelae in Carbon Monoxide Poisoning, J. A. M. A. 106: 669, 1936.
[1078] Bernstein: Hautnekrose bei Kohlenoxydvergiftung, Zbl. 44: 6 6, 1933.
[1079] Oppenheim, G.: Umschriebene Hautgangrän und Purpura nach Leuchtgasvergiftung, Zbl. 42: 161, 193
[1080] Siffert, F. A.: Factors in Peripheral Skin Lesions Following Carbon Monoxide Poisoning, J. M. Soc. New Jersey 40: 418-4 0, 1913.

develop into deep sharply outlined round ulcers or patches of dry gangrene Such necroses have been seen on the heels soles, ankles calfs sacral area fingers and scalp In several cases an entire limb was affected [1081, 1082]

Perhaps decubitus is at least in some cases a factor in the pathogenesis of the ulcers but there are clinical and histological reasons to blame primary vascular damage instead

Herpes zoster especially of the forehead is considered to be a characteristic sequel of monoxide poisoning[1083] (Schas in discussion to Fischel[1084])

Sedatives

The *barbiturates* quite frequently produce *rashes* of allergic character Pruritus and urticarial macular, scarlatiniform, multiform or petechial exanthems are fairly common and well known especially from phenobarbital Bullous eruptions in the mouth have also been observed [1085] The severe and in some instances fatal cases of exfoliative dermatitis are fortunately very rare [1086]

Nirvanol is a hypnotic which almost constantly produces a morbilliform *exanthem* after 6 to 14 days of regular administration The rash is accompanied by conjunctivitis stomatitis and other mucosal reactions fever cyanosis dizziness and other nervous symptoms gastrointestinal and hepatic symptoms and albuminuria a syndrome which is known as *nirvanol disease* (V Pfaundler after R L Mayer[974]) Nirvanol is used in the treatment of chorea The therapeutic result depends on the development of the nirvanol allergy [1087]

Bromine

Morbilliform urticarial bullous vesicular vacciniform and other *rashes* are occasionally seen after the administration of bromide More characteristic are acneiform eruptions which appear at the predilection sites of acne vulgaris especially on and around the nose It seems that bromine acne is more apt to suppurate and to form flaccid pustules than the common juvenile form [1088]

In some cases *ulcers* form which by central healing and partial peripheral advance may resemble tertiary syphilis A peculiar feature of some bromine reactions is the tendency to develop *tuberous* or tumor like vegetations These bromodermas are known in several varieties and combinations They occur as papillomatous confluent crustous suppurative or ulcerating sessile or tuberous usually painful eruptions Small subepidermal abscesses in the edges of the lesions may create a blastomycosis like picture After the expression of pus from large lesions a quite characteristic cribriform surface results [1089]

[1081] Fuz r S and Spilberg S Gangr n of Low r Extremity Foll wing Carbon Monoxide Asphyxia Am J Clin Path 16 111 116 1946

[1082] Drinker C K Carbon Mo oxide Asphyxia New York 1938 O ford Uni ersity Press

[1083] Knapp A S ltene Fälle von H pes Zoster München med Wchns hr 87 558- 89 1940

[1084] Fischel Fälle von Hautveränd rungen bei Leuchtgasvergiftung Z11 1 109 10 1

[1085] Hoffm n M Ph nobarbital Eruption of the Mouth Arch Dermat & Syph 25 983 1932

[1086] Jontofsohn K Ueber Barbitursäure-All rgie Med Klin 29 180 191 1933

[1087] Madd n J F Nirvanol Eruptions Arch Dermat & Syph 28 1065 1073 193

[1088] Kierberg L Toxicod rmi n Handb d H u Gk 4 2 253-376 193

[1089] Neth rton E W Nodular Papillomatous Bromod rma Cl veland Clin Quart 12 10-?? 1945

The bromodermas are most often seen on the lower legs and vary widely in size and number of lesions There may be a few or several hundred and some may be as small as peas while others may reach the size of a fist [1088] The various types of lesions may be seen in the same patient at the same time A characteristic *foul odor may be present* [1089]

The lesions have occasionally been first observed several months after the ingestion of bromine had been discontinued Bromoderma sometimes develops out of other pre existing skin lesions e g ulcers scars and injuries The tongue and other parts of the mouth may participate in the fungating process

The *allergic* character of the bromodermas has been recognized by most authorities but is disputed by some investigators[1090] mainly because of negative skin tests



Fig 156 —Acneiform eruption from bromine

The passive transfer of the allergy to the guinea pig has occasionally been demonstrated [1091] Bloch and Tenchio[1092] elicited in their case of severe bromoderma with fatal outcome positive patch tests after 24 hours Later these reactions turned into bromoderma an interesting demonstration of Koebner s phenomenon [1093] Positive scratch and intradermal tests have also been elicited [1094] Excessive eosinophilia is another argument in favor of the allergic nature of the bromodermas The vegetations have several times been found to be free of bromine The diagnosis of the bromine dermatoses has to consider such heterogenous diseases as the acute exanthems acne vulgaris syphilis blastomycosis epithelioma mycosis fungoides erythema nodosum and others

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[1090] Lehner E Bromoderm Zbl 53 78 1936
[1091] Soroka F I Bromoderma Vegetans Venerol i dermat 8 52 56 1931
[1092] Bloch B and Tenchio F Bromoderma Vegetans Arch f Dermat u Syph 165 93 148 193
[1093] Hassmann K Bromoderma und Hautallergie Arch f Kinderh 110 103-107 1937
[1094] Bernhardt R Acne bromata provocata Arch f Dermat u Syph 171 11 114 1934



Fig 157 —Bromod rma tubero um (From Netherton E W Cl veland Clin Quart)

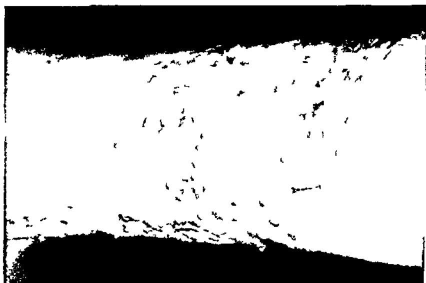


Fig 158 —Bromod rma tuberosum From Netherton E W Cl v lan l Clin Quart)

The copper or brownish hue of the bromodermas is often emphasized

Discontinuation of the bromides and large amounts of fluid and sodium chloride[1095] are important in the *treatment*

The *prognosis* of treated cases is generally favorable if the use of bromides is discontinued Scarring and pigmentation are common sequelae Rarely the lesions continue to develop despite discontinuation of the drug and treatment Such cases may end fatally [109]

Iodine

The eruptions following the internal use of iodine and its compounds follow the pattern of those produced by bromine Acne is the most common dermadrome of iodism Vesicular bullous [1096] and hemorrhagic eruptions have been seen more often than the vegetating forms The allergic nature of the iododermas and the sensitizing effect of iodized table salt[1097] has been established by experimental investigations [1098]

Fatal cases of iododerma tuberosum are very rare [1099 1101]

Some Other Drug Eruptions

Almost all drugs and poisons are able to produce allergic skin eruptions Among the great number of multiform morbilliform scarlatiniform eczematoid hemorrhagic bullous vesicular and other exanthems a few stand out because of unusual clinical features

Phenolphthalein eruptions are well defined round or oblong red and later purplish brown spots They sometimes appear as large bullae The macular lesions are lentil to palm sized and are most often seen about the buttocks and the lower back but also on the extremities

The bullae are large and deciduous leaving an erythematous and pigmented base Eczematous forms are less well known The lesions may after an inflammatory stage recede and leave only a faint pigmentation It is a peculiarity of the phenolphthalein eruptions to appear in exactly the same sites even after complete or almost complete disappearance and after long intervals This is known as a *fixed eruption*

[1095] Wil [illegible] J Further Contributions to the Experimental Aspects of Iodid and Bromid Exanthem Arch Dermat & Syph 8 407-410 1923

[1096] Spillm [illegible] W ls and Malton D mite bulleu généralisé d origine iodique chez une hémiplégique Bull Soc franç de dermat et syph 40 1554 1556 1033

[1097] Bech [illegible] I F Iodized Table Salt as an Etiologic Factor in Iododerma Arch Dermat & Syph 29 529-536 1934

[1098] I iu hi C Eine [illegible] Iodo m v Jode anth m Jap J Dermat 32 130-131 1932 Zbl 44 3 [illegible]

[1099] Hand [illegible] I and F [illegible] ma G H Fatal Iododerma Arch Dermat & Syph 34 [illegible]9-241 1036

[1100] H [illegible]zeberg H and Maschkilleisson L Ueber Thromboangiitis obliterans (Beitrag zur Pathogenese des Iododerma bullosum vegetans) Beitr z path Anat u z allg Path 94 353-360 1934

[1101] Ell[illegible] J J and F x F C Fatal Iododerma Arch Dermat & Syph 24 745-757 1931

Phenolphthalein is an ingredient of more than a hundred proprietary laxatives [110] Similar fixed eruptions also occur as a reaction to *antipyrin* [1103] The eruption to either drug may develop within an hour after ingestion Severe melanoderma after phenolphthalein is very rare [1104]

Sedormid a mild sedative of the urea group has in many cases caused severe thrombocytopenic purpura [110] [1107]

Veramon a popular European combination of barbital and amidopyrin may give rise to fixed symmetrical eczematous patches and mucosal swellings Its use has been discouraged because of the danger of *agranulocytosis* from the amidopyrin content

Quinine eruptions are most often scarlatiniform In severe cases exfoliative dermatitis may develop Severe purpura is a rare event About one out of 200 patients is or becomes allergic to quinine [1108]

Atabrine which proved to be a satisfactory substitute for quinine may cause a lemon to sickly greenish yellow discoloration[1109] after one to four months of use The yellow dyschromia is uneven in contrast to icterus with the heaviest discoloration on the exposed parts and in the folds of the body The sclerae remain white The extensor[668] surfaces of the arms and feet the webs the nape the forehead and the circumoral area are most deeply stained A golden ring around the mouth is a peculiarity of the atabrine pigmentation Unlike the discoloration in carotinemia the palms are less yellow than the dorsa of the hands

Bluish pigmentations have been seen in the hard palate epiglottis tracheal rings and the nail beds

During the war in the South Pacific especially in New Guinea many cases of a dermatosis with features both of an *atypical lichen planus and eczematoid dermatitis* occurred among the troops who took atabrine regularly for the suppression of malaria but it is not generally recognized that atabrine is the cause [1110] The condition is characterized by various combinations[1111] of purplish hypertrophic lichenoid papules and plaques frequently with a rough verrucous surface and eczematoid plaques in all stages of erythema oozing and scaling

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[1102]Belote G H and Whitney H A K Phenolphthalein Compounds Arch Dermat & Syph **36** 279-281 1937

[1103]Basch G and Sainton J Plaque érythémato-pigmentée fixe et éléments bulleux à type d'érythème polimorphe par ingestion de cachets à base d'antipyrine Bull Soc franç de dermat et syph **42** 453-455 1935

[1104]Weiss R S Dermatitis Medicamentosa (Phenolphthalein) Arch Dermat & Syph **23** 118 1931

[1105]Falconer E H and Schumacher J C Purpura Hemorrhagica Due to Ingestion of Sedormid (Allyl Isopropyl acetyl-carbamide) Arch Int Med **65** 1 137 1940

[1106]Loewy F E Thrombopenic Hemorrhagic Purpura Due to Sedormid Allergic Effect Lancet 1934 1 845-846

[1107]Huber H Case of Purpura Hemorrhagica Resulting From Sedormid J A M A **113** 674 675 1939

[1108]Haue A Ueber Chininintoxikation und Chinidiosynkrasie D utsch med Wchnschr **61** 332-336 1935

[110] Schechter A J and Taylor H M Atabrine Pigmentation A J M Sc **192** 643-650 1936

[111] Epstein F Lichen Planus-Eczematoid Dermatitis Complex of Southwest Pacific Bull U S *Army M D pt 5 689-693 1945*

[1111]Untoward Reactions Attributed to Atabrine (Atypical Lichen Planus) J A M A **129** 1091 1093 1945

The dermatosis may also though rarely consist of lichenoid elements alone More frequently the eczematoid lesions dominate the picture entirely even to the extent of severe generalized *exfoliative dermatitis*

The legs and forearms the dorsal surfaces of the hands and feet and the face neck buttocks and genitalia are predominantly and symmetrically affected Atrophy and hyperpigmentation nail changes and shedding of the nails patchy alopecia and dyshidrosis have been described as late sequelae

With the exception of severe exfoliative dermatitis the course is generally benign if atabrine is discontinued

Picric acid may cau e generalized *yellow discolorations* which simulate icterus The sclerae take part in the staining

The *sulfonamides* may cau e a great variety of eruptions which are es entially the same as those due to the barbiturates the arsphenamines and many other drugs A special feature is the frequent *photo sensiti ation* caused by the u e of sulfonamides

Ephedrine besides occasionally causing generalized erythemas and dermatitis has in some persons a tendency to produce urticaria and local swellings especially of the eyelids [111 1114]

Codeine rashes [115] have been described as follicular erythemas which quickly develop into scarlatina like exanthems Codeine and opium occasionally produce pruritus or formication [1116] Paresthesias are also a dominant symptom in chronic *ergotism* from[1117] Claviceps purpurea infected rye and wheat and in ustilaginism from corn infected with Ustilago maydis [1118] Even acrodynia like cases of morbus cerealis have become known In *favism* a severe poisoning occasion ally caused by the eating of broad beans (vicia faba) purpura is an important symptom [1119]

Dinitrophenol the dangerous weight reduction agent caused urticarial macular maculo papular and eczematoid rashes in 7 to 20 per cent of the treated persons [11 0 1L1] The frequent *yellow discoloration* is due to the staining and is not caused by icterus [668 1122]

[1112]Bullen S S Iran L N and Larker J M Dermatitis Medicam ntosa Due to Fphedrine J All rgy 3 48 -488 193

[1] Ay es S Jr and An lerson N P De matitis Medicam ntosa D e to Ephedrin J A M A 97 437-440 44 -443 1931

[11 1]Abram witz F W and Noun M H Ephedrine Dermato es B It J Dermat 45 2?-?37 1933

[1 15]Scheer M ar 1 Kell H The Skin Fruptions of Codein J A M A 102 908 910 1934

[1116]Gold mith W N Significane and Treatm nt of It hing Practitioner 142 36 54 1939

[1117]Kau itz J Chroni End mi E goti m It R lati n to the Vasomoto and Trophic Dis a es Arch Int Med 47 548 64 1931

[1] May hof r E Ustilagi i mus eine bish r unbeka nte Form alim tär r Stö ung bei ler Mal ernährung im Kind alter Med F egl 6 153 157 1931 Z11 39 ? 6

[1] Jim n Diaz C and Hol C M Anaphylacti Purpura Due to S nsitization to Beans (Purpuri Form of Favism) R v clin espan 5 1 9 130 194

[112] Frumess G M Allergic R a tion to Dinitroph nol (Case) J A M A 102 1 19 19 0 1934

[1121]Kesten B M Dermatiti Medicam ntosa Fo mula 81 (Dinitrophenol) Ar h D rmat & Syph 31 73 75 193

[1122]Simkin S Di itrophe l and D siccated Thyroid in Treatm t of Obesity J A M A 103 110-?117 ?103 199 193

CHAPTER XIV

DISORDERS OF THE CIRCULATION

Heart Disease

Cardiac decompensation no matter what its cause may be produces a rather uniform syndrome with dyspnea cough palpitation and precordial distress dominating the complaints Cyanosis and edema are almost always present

Cardiac Decompensation —*Cyanosis* is not only caused by the deficient blood circulation If the state of decompensation lasts for some time the respiratory system suffers and the oxygenation of the venous blood becomes insufficient increasing the cyanosis Cyanosis is an early sign of valvular heart disease especially of the right heart but also though later of the mitral valves It is less pronounced in aortic insufficiency [85]

Extreme degrees of cyanosis are encountered in the *newborn* infant with *congenital affections of the heart* *In contrast to the cyanosis in acquired and* adult types of heart disease the blue discoloration may cover the entire body surface of the baby (Morbus caeruleus) In later life the cyanosis is usually restricted to or at least most marked in the acra The cheeks the lips the nose the ear lobes the finger tips the toes the elbows and the patellae are chiefly affected [13] Frequently only a slightly purplish hue of a seemingly healthy complexion indicates an underlying cardiac insufficiency The cyanotic parts especially the feet and lower legs are cool

If cyanosis exists for a longer period sharply drawn *telangiectases* appear On the face they resemble rosacea or they are the first stage of rosacea Telangiectases occur also on other parts of chronically congested skin e g between the shoulder blades and on the abdomen [11 3]

Edema usually is seen first in the skin about the ankles but later it may involve the entire skin and the subcutaneous tissues Chronic congestion may cause *clubbing* of the fingers and toes more so in children than in adults [11 3]

The skin in chronic congestion is if not yet cyanotic *pale* and often grayish Slight *hemorrhagic* tendencies are an early sign of decompensation though they may be only detected by the tourniquet test or the capillaroscope [11 4] Naegeli mentions extravasations over the thorax and epigastrium in decompensated mitral insufficiency

The *pallor* of the patients with mitral stenosis before the cyanosis occurs is marked [13]

Hyperpigmentation occurs—especially in children—on the forearms and the dorsa of the hands and fingers The pigment is hemosiderin from the extrava a

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[11 3] Seck I H Chronisch Stauungshaut beim Kind Monatschr f Kinderh 45 394-403 19 ?
[11 4] Jürgensen F Okkulte Hautblutungen Deutsches Arch f klin Med 176 ? 0- 4 1934

tion [1143 115] Slight *jaundice* is frequent It appears less pronounced in the edematous parts [85] Increased *freckles* are often seen in juveniles with decompensated mitral insufficiency [1126]

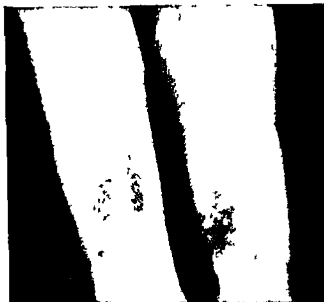


Fig 159 — Myocarditis Dermatitis of leg exacerbating and receding with cardiac decompensation



Fig 160 — Dermatitis of the leg in hypertension Parallelism of exacerbation with degree of cardiac decompensation

[1126] Kaufmann F Die pathologischen Pigmentierungen der Haut Handb d H u Gk 4 ? 1011 1221 1933

Hypertrichosis is a symptom of chronic congestion in children The back the face and the extensor aspects of the extremities exhibit the increased lanugo most distinctly[1123]

Eczema of the lower legs sometimes with a purpuric component is an occasional accompaniment of decompensation The healing with improvement of the circulation and relapse on recurrence of decompensation is proof of the circulatory factor in these eczemas

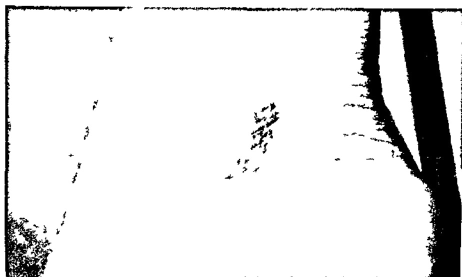


Fig 161 —Schamberg's dermatosis in circulatory stasis (Courtesy Dr M Jessner)

The *pulsating erythema* of the nail bed or of a dermographic line known as the capillary pulse is a well known sign encountered in aortic insufficiency but also in other conditions The jerking pulsation can be demonstrated in the capillaroscope[1126]

Arteriosclerosis, Hypertension

Arteriosclerosis affects the arteries of the skin[1127] as well as those of other organs (see Chapter on Old Age) The capillaries appear tortuous and thin in the capillaroscope (E Weiss after B Niekau[1126])

The clinical skin changes produced by arteriosclerosis are best observed in the *feet*[1128] The skin is dry due to the impairment of the glandular functions The *nails become atrophic and brittle or thick Corns and calluses become thicker* The lanugo hair on the dorsa of the phalanges disappears The foot including the sole may become cyanotic on dependence and pale on elevation

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[1126] Niekau B Kapillarbeobachtungen an der Körperoberfläche des Menschen Ergebn inn Med u Kinderh 22 479-551 1922

[1127] Wiedmann A Beiträge zur Pathologie der Gefässerkrankungen der Haut III Mitt Die Arteriosklerose der Haut Dermat Wchnschr 102 69 75 1936

[1128] Nomland R Cutaneous Manifestations of the Circulatory Disorders of the Foot J A M A 124 747 750 1944

Nomland[11 8] believes that the more nearly horizontal the leg is when pink color returns the greater is the insufficiency of the arterial supply Wounds and infections even trivial ones heal slowly and may cause severe complications This is the more important since *pruritus* is a common symptom of cutaneous arteriosclerosis and decompensation [1129]

Cardiac infarction may leave its mark in cross furrows of the *nails* (Beau s lines) or more rarely in transversal white lines [1130] Cross furrows have also been observed on the toenails in intermittent claudication [1131] Occasionally an *erythema* of the face and neck resembling erythema pudoris has been seen in *angina pectoris*[113] and *hypertension* [1133]

Herpes Zoster intercostalis has often been related to angina pectoris [13 1136]

The most important though by no means constant cutaneous manifestation of hypertension is *pruritus* It is often severe and reflects in its intensity the ups and downs of the blood pressure Severe attacks of pruritus may precede apoplectic episodes Rarer than pruritus alone are *eczematous* or *pruriginous* changes It is in such cases hard to decide whether the dermatosis is due to hypertension nephro is or decompen ation since it may accompany all of the e conditions The eczema sometimes seems econdary to prurigo the itching papu lourticarial lesions of which are quickly destroyed by scratching A slight scab covered spot of lentil to fingernail size ensues Groups of such lesions in various stages of development and lichenification are usually found along the legs and in some severe cases over the entire body These ca es are at least temporarily benefited by superficial X ray therapy

In obstinate cases of eczema of the hands of nummular eczema and of scaling and itching of the finger tips one should consider the state of the circulation and treat accordingly

Hypertension aortitis arrhythmia chronic glomerulo nephritis and other vascular and hepato splenic disorders may be accompanied by pigmented and depigmented hemorrhagic inflammatory plaques on the lower legs Favre[80] and his collaborators have stressed the internal relationship of this condition which he called *angiodermatitis pigmentosa purpurica* He stressed that this common syndrome has nothing to do with varicose veins and that it does not show the features of eczema The underlying periosteum is often early affected The patches run a gamut of colors from yellow to blue black The surroundings are often depigmented The lesions are also variable in size and contour Hemorrhagic infiltration with formation of a black scab and ulceration occurs

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[1129] Coh G Pruritu al dyspnoisches Symptom mit B m kung n übe pru ig e Summation Arch f Dermat u Syph 148 3 19

[113] I rbach F Whit Cross Striae of the Finger Nails Followi g Ca diac Infarction Arch Dermat 52 106 107 194

[1131] Schlesinger H Das N g l ymptom I i lem I termitti d n Hink n Med Klin 26 921 922 1930

[1132] Portorali A an l Fl ra G T Angine d poitrine d effo t avec érythème initial et pou sée hypertensi e, Bull t m n d Soc med H{p I Paris 47 16 0-1659 1931

[1133] Weber F P Da wi 1 Blotchy Flushing Ov r Neck and Upper Thorax in an Eld rly Woman With High Blood Pressur Proc Roy Soc Med 28 31 103

[1135] e rio J Herpes ost r b i l ren Organ krankung n Deutsche, med Wchnschr 62 900-903 19 6

Tenderness and scaling are other features The pigment is hemosiderin In spite of some similarities the common angiodermatitis is to be separated from Shamberg s disease and from purpura Majocchi Syphilis is the most common etiologic factor

The compression of the superior vena cava by an *aneurysm* of the ascending aorta may cause congestion and tortuosity of the veins of the neck and face even of almost the entire upper half of the body There is also edema and cyanosis Pressure on one of the innominate veins produces these signs on one side only usually the left[13] A leaking aneurysm of the abdominal aorta may cause huge suggillations of the scrotum and lumbar area



Fig 162 – Female aged 17 years Arteriovenous aneurysm following fracture of radius Increased growth of the affected hand large pseudohemangiomatous coiled vessels increased skin temperature hyperidrosis and bruits (Patient of Dr Karl Schlaepfer)

Peripheral arterio venous aneurysms are usually caused by trauma They cause hemangioma like accumulations of tortuous blood vessels with pulsation and murmurs The skin over such a lesion is warmer than normal and perspires more readily The increased blood supply causes increased growth of the involved part including the bones

Thrombo-Angiitis Obliterans (Buerger s Disease)

In this disorder of unknown but[1136] probably bacterial etiology[1137] the peripheral arteries and veins of the legs rarely of the arms—sometimes together with adjacent nerves[1138] are affected Arteritis with thrombus formation in single or

[1136] Buerger L The Circulatory Disturbances of the Extremities Philadelphia and London 1924 W B Saunders Co

[1137] Allen E V Thromboangiitis Obliterans Bull New York Acad Med 18 16 189 1942

[1138] Klaer S Thrombo-Angiitis Obliterans (Buerger) Acta orthop Scandinav 2 103 13 1931 Zbl 29 50 1931 193

multiple foci causes a state of ischemia with severe pain. The pain may occur on exertion and then it has the character of intermittent claudication or it may be experienced while the patient is at rest. In this case the pain is continuous, worse at night and sometimes aggravated[1137] and sometimes eased by dependency. Gangrene with severe pain may occur. The course of the disease is most often chronic and slowly progressive in attacks. The peripheral pulses in the affected limb are absent or diminished. The sufferers are almost exclusively young men (98 per cent) often Hebrews (28 per cent) and heavy cigarette smokers (93 per cent).[1139] Familial incidence has been observed.[1140]

Dermadromes.—The skin[141] of the toes is, at least in the fairly advanced stages, moist, cool, often scaly, tender and reddish blue in patches, especially if the patient stands. *Elevation* blanches the limb. Reactive hyperemia is apt to follow on lowering the leg except in severe cases.[1138] If the time required for the return of color while in the dependent position is longer than 10 seconds, impaired arterial circulation exists. In marked impairment of the arterial circulation by thrombo-angiitis the return often takes more than forty five seconds.[1137] Refilling of veins after emptying by elevation also takes longer than ten seconds. Superficial palpable *phlebitis* is a feature in Buerger's disease which leaves *hemosiderin pigmentation* for a long time after healing.

Variable degrees of *pallor or cyanosis* may follow exposure to *cold* or *emotion*.[1137] If *gangrene* develops it is less extensive than in arteriosclerosis because of the smaller caliber of the thrombosed arteries. It is usually of the moist type. The endangered toes are bluish, especially the nailbeds. The skin is often glossy and atrophic. Subungual keratosis develops frequently. Ulceration of the big toe is the commonest form of necrosis. Gangrene of the fingers is much rarer than gangrene of the toes since the establishment of collateral circulation has a better chance in the arms than in the legs. Besides the occlusion by thrombosis, vasospasm plays a part. The diagnosis has to exclude arteriosclerosis. Here the picture is very similar but the patients are older, the pain at rest is milder, gangrene is more apt to be dry, and phlebitis and edema are not features. Lipemia is frequent in arteriosclerosis and the arteriosclerotic artery may be detected by X-ray.[1137]

The *treatment* requires complete abandoning of smoking, vascular exercise by systematic raising and lowering of the legs, and warm baths. Mechanical pulsating devices do not seem to be very effective in Buerger's disease. Amputation, nerve section or sympathectomy are often necessary.[1137, 1141]

Shock

Shock is characterized by circulatory failure and deep depression of the nervous functions. It may be caused by trauma, hemorrhage, massive infection, burns, intestinal perforation, cardiac failure and other conditions.

[1139] Horton, B. F.: Thrombo-Angiitis Obliterans, 948 Cases, Incidence of Amputation. Mil. Surgeon 84: 599-600, 1939.

[1140] Mészáros, K.: Arteriitis obliterans (Thromboangiitis Buerger) als familiäre Erkrankung. Deutsche Arch. f. klin. Med. 171: 391-396, 1931.

[1141] Homans, H.: Circulatory Diseases of the Extremities. New York, 193), The Macmillan Company.

In shock the effective circulating blood volume i e cardiac output and venous return is reduced and the peripheral flow of blood is slowed down[114] The blood pressure is at first maintained by vasocompensatory mechanisms but drops as soon as these mechanisms become weak While in the initial or pre monitory stage of shock the pulse may not be altered it becomes rapid and thin in the fully developed syndrome

Dermadromes —Di Palma[1141] stresses the diagnostic importance of the skin phenomena in the initial phase the knowledge of which may enable the physician to apply help before the onset of deep shock For the examination the patient has to be stripped and remain exposed to room temperature for at least 10 minutes If the skin can be blanched by pressing the forefinger forcibly into it some blood must be in the skin The color contrast with the unblanched skin and the rate of fill in of the blanched areas permit quick though rough and unreliable estimate of the peripheral blood flow Gentle touching with the back of the digits permits the determination of gross differences between the skin temperature of the trunk and the extremities Such differences would indicate a slow blood circulation in the periphery The color of the skin is an excellent guide in the estimation of the rate of the peripheral blood flow It should be judged by the hue of the cheeks the lips and especially of the nail beds Di Palma[1142] advises the acquisition of competence by observing the nail beds under controlled conditions of circulation produced by a blood pressure cuff and varying elevation of the arm Brick red purplish and finally deep purplish blue in dicate the degrees of peripheral circulatory failure

Since the brick red hue is an early sign it is most important Simultaneous forcible stroking of the skin with a blunt instrument on the chest and on the fore arms provides an opportunity to compare the differences between the time of *appearance and the color of the red dermographism* The peripheral blood flow must be considered slow if the red line appears later than five seconds and if the reaction on the forearm is delayed in comparison with the chest The color should be bright red DiPalma Muss and Foster[1143] have devised a method which measures the minimal time required to elicit hyperemia by a weighted rubber ring placed on the skin of the chest and arm (stimulus time) and the time after which the hyperemia fades (clearance time) These times are compared with those obtained from a normal person in the same room

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[1142] DiPalma J R The Circulation in the Skin in the Shock Syndrome J A M A 123 691-693 1943

[1143] DiPalma J R Muss I and Foster F I Reactive Hyperemia Ring Test in the Study of Pedal Lesions Caused by Arteriosclerosis Obliterans and Arterial Embolism Am Heart J 24 31 361 191

CHAPTER XV

DISEASES OF THE KIDNEYS

The relation of dermatoses to renal disorders fascinated the physicians of the nineteenth century more than the recent generations. Bright in 1827 was convinced of the sympathy between the skin and the kidney and many famous authors have investigated this relationship more closely.[36]

The kidneys being concerned with the excretion of water soluble substances are functionally linked to the skin. Under normal conditions the skin stores about 28 per cent of the body's water. It takes up much more in edema[1144] which is the dominant symptom in acute diffuse glomerulonephritis and in some stages of other renal diseases. The loose texture of the skin and of the subcutaneous tissue affords more storage space than the muscles or even the serous cavities are able to provide. Along with water the skin stores chlorine and minerals. The vast vascular capacity of the skin provides an important regulating mechanism of the blood pressure which is the main power behind the urinary excretion. The skin has an excretory function which however can only partially and occasionally replace renal excretion.[1145]

Under normal conditions the skin as well as the kidneys excrete about 1300 c c of water daily but the kidneys are able to concentrate from the blood more than thirty times more urea and three times more NaCl than the tubules of the sweat glands. Thus even a damaged kidney usually excretes better than the skin and the skin alone is not able to replace the function of the kidneys.

Dermadromes were seen in approximately one fifth of the series of 1100 patients with all forms of nephritis and nephrosis studied by Chargin and Keil.[36] These authors found that skin diseases occur more frequently in association with *azotemia* than in those without azotemia. In contrast to earlier observers[1146] they found that *purpura* is the most frequent lesion associated with nephritis. All types of hemorrhagic lesions ranging from pinpoint petechiae to large extravasations were encountered. Chronic glomerular nephritis without edema seemed to predispose to hemorrhage far more than the other clinical types of *nonsurgical kidney disease. Higher degrees of azotemia often cause intense* purpura. Sometimes the hemorrhagic tendency expresses itself only in a hemorrhagic component of a usually nonhemorrhagic dermatoses e g tinea. *Pruritus* varying widely in intensity and in its sequelae may be the first symptom of nephritis (Oienlatory after Pringle[1146]). It occurred in 20 per cent of the cases of essential hypertension with azotemia and in 12 per cent of the instances of

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[1144] Kroetz C Die klinischen Zusammenhänge zwischen Haut und Nierenkrankungen Zbl 42 39 193

[1145] Flimmer I Schwitzkuren Verhandl d Gesellsch f Verdauungs u Stoffwechselkr 13 212 1937

[1146] Pringle J J Skin Eruption in Bright Disease Practitioner 117 540 1901

chronic glomerular nephritis with edema Its infrequency in all other groups of the series of Chargin and Keil[3 6] is striking Azotemia is probably the inciting factor Azotemia without pruritus occurs but if pruritus is present in uremia it is regarded as of serious prognostic importance[3 6] The pruritus may be explained by *dermatitic changes* which Rossle observed in almost all of 25 cases of



Fig 163 – Purpura Chronic nephritis

uremia even when no gross changes were present[1147] These inflammatory changes ranged from simple perivascular infiltration to necrotic and herpetiform pandermatitis The findings could not be confirmed entirely in an American series[1148] Here atrophy of the skin was the dominant pathologic feature Other pathologists have cautioned not to overrate the perivascular infiltration in the skin[1149] which is often seen in glomerulonephritis

The *urea* content of the skin is usually high The appearance of crystalline urea as a thin white saltlike deposit on the skin especially about the nose the

[1147] Rössl R Urämisch Dermatiti Virchow Arch f path Anat 271 304-316 19 9
[1148] Rosenthal S R Uremic Dermatiti Arch Dermat & Syph 23 934 1931
[1149] Herxheimer G and Roscher W Hautveränderungen bei Nephritis Münch med Wchnschr 65 14 1918

neck and the shoulders[1148] is known as *urea* (uremic) *frost* It occurs most frequently in malignant sclerosis and essential hypertension (10 to 20 per cent after Chargin and Keil[3 6]) A prolonged agonal period which allows the formation of the crystals together with a high urea content of the blood and of the skin seem to be the factors accounting for its relative frequency in these conditions[3 6] The phenomenon of urea frost is more often seen post mortem than in life It is still controversial whether the source of the urea frost is the sweat glands or the sebaceous glands Its accumulation in the areas of accumulated sebaceous glands and its absence on the palms and soles seems to support the sebaceous gland theory while observations of crystals at the mouth of the sweat glands seem to prove the sweat gland origin Urea frost is of ominous prognostic significance

Erythematous bullous and urticarial eruptions in nephritis[49 1150] have occasionally been described Generalized exfoliative dermatitis is also mentioned in connection with the renal disease[1151] Some of these dermatoses may have been caused by septicemia Ehrmann[115] saw in edematous patients aggregated vesicles about the head which rapidly formed oozing pink surfaces

Fissural *eczema* is supposed to be more common in nephritis without edema Grouped papular eruptions of great obstinacy were in the older literature known as erythema papulatum uremicum[49] (Merk after Ehrmann[115])

It may be mentioned in this connection that rabbits with experimental glomerular nephritis could be shown to be more sensitive to skin irritation from tar than the normal controls[1153]

A progressive febrile dermatosis probably of bacterial origin occurring relatively often in *lipid nephrosis* is referred to as *erysipeloid* (This condition should not be confused with the erysipeloid of Rosenbach) The eruption is seen on the abdomen and thighs spreading from there with an erythematous circinate flush and tender border There may be recurrent attacks[1154] with occasional abscess formation[1155]

The complexion of patients suffering from *contracted kidney* is often yellowish This discoloration is restricted to parts exposed to light The pigmentation is explained[1156] by the retention of urochromogens which under the influence of light change into their color just as they do in a pale urine from an arteriosclerotic kidney There is no retention of urochromogens in acute nephritis

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[1150] Sachs O Erythema exsudativum multiforme und Erkrankungen innerer Organe Arch f Dermat u Syph 98 35 7? 1909

[1151] Duckworth D A Case of Chronic Interstitial Nephritis in Which Dermatitis Exfoliativa Supervened Brit J Dermat 12 1900

[115] Ehrmann S Beziehungen der Ekzematosen Erkrankungen zu inneren Leiden Halle 1924 Carl Marhold

[1153] Christianof S A La réaction de la peau à la fonction des reins Ann de dermat et syph 7 685-01 1936

[1154] Aldrich C A and Boyle H H Erysipelas Like Lesions of Skin in Nephrosis Am J Dis Child 56 10 0 1938

[1155] Schwarz H and Kohn J L Bacteremia and Skin Manifestations in Lipoid Nephrosis Am J Dis Child 38 62 774 1929

[1156] Becher E Untersuchungen über das Zustandekommen der gelblichen Hautfärbung bei Nierenins suffizien Münch med Wchnschr 77 19 ? 1930

Carotinemia is always present in nephroses but only in 10 per cent does the skin become noticeably yellow [1157]

In acute nephritis the *capillaroscope* may reveal narrow arterial and wide tortuous venous segments The subpapillary venous plexus is well visible and the circulation is slowed These changes may precede the outbreak of nephritis[170] (Goth after Niekau[11 6]) suggesting the primarity of the capillary damage

Herpes zoster has often been seen in attacks of *nephrolithiasis* [1135] Severin[113] found that these eruptions corresponded to the eleventh and twelfth dorsal and the first and second lumbar segments Their area was found identical with the associated Head s zones Some cases of *pruritus* and *obstinate eczema* in chronic nephrolithiasis were relieved by operation They can be interpreted as caused by the infected focus and by parenchymal damage caused by calculi and infection

Pruritus is a common symptom in all types of chronic urinary *retention* Thus it is frequently and early observed in benign hypertrophy of the *prostate* and occurs also in stricture of the urethra It is good advice to examine prostate and bladder in all unexplained cases of pruritus and secondary pyoderma present in elderly men [13 1158] In rare instances pruritus vulvae may be caused by nephroptosis [1159]

Though not being the cause of dermatoses *Peyronie s disease* or induration of the tunica albuginea of the corpora cavernosa penis is possibly a manifestation of a systemic disorder which may also cause surface symptoms Touraine and Ruel[1160] call hereditary polyfibromatosis the tendency to form nodular nonencapsulated indurations in many parts of the connective tissue While the association of induration of the corpora cavernosa with Dupuytren s contraction of the palmar aponeuroses has long been recognized keloids fibromas of the fingers and similar connective tissue lesions are also seen together with Peyronie s disease Simple dominant heredity is supposed to exist Similar hypotheses of earlier authors have not found acceptance [1161]

[1157] Boeck W G and Yater W M Xanthemia and Xanthosis (Carotinemia) J Lab & Clin Med 14 1129 1143 1929

[58] Lutz W Stoffwechs I und Haut Handb d H u Gk 3 1929

[1159] Strickler A Ptosis of a Kidney as a Cause of Pruritus Vulvae Arch Dermat & Syph 50 405 1944

[1160] *Tourain A and Ruel H Hereditary Polyfibromatosis A n de Dermat et Syph 5 1 5 1945*

[116] Ned lan I W Dupuytren sche Kontraktur und Beruf Arch f C w b path u Gew rl hyg 2 3-43 1932

CHAPTER XVI

DISORDERS OF THE ENDOCRINE GLANDS

THE PITUITARY BODY

The hormones of the *anterior lobe* of the pituitary stimulate the activity of the thyroid the parathyroids the mammary glands the islands of Langerhans in the pancreas the adrenal cortex the gonads and the placenta The carbohydrate and fat metabolism and the growth are influenced either directly or indirectly by the effects on the above named glands [116, 1163]

The *intermediate lobe* activates the melanophores in the skin of amphibia Its physiology in man is little understood

The *posterior lobe* secretes two principles which act on the smooth muscle fibers It profoundly influences diuresis by the production of an antidiuretic hormone

Frohlich's Syndrome

Dystrophia adiposogenitalis or Frohlich s Syndrome is the triad of obesity, particularly of the lower trunk genital underdevelopment and pituitary symptoms The latter seem due to hypoactivity of the anterior lobe and the pars intermedia Frohlich s Syndrome is one of the commonest endocrine diseases especially of young males This was demonstrated in the induction centers during the last war [116]

Dermadromes —In the younger patients the skin is smooth and pale and the veins are well visualized Cushing remarks that persistent freckles on exposed areas is a characteristic of most cases of hypopituitarism Perspiration is scant or lacking [1165] The subcutaneous fat which is particularly abundant on the hips sometimes seems to suggest a deep seated nonpitting edema Striae are seldom seen The pubic and axillary hair is absent and the lateral third of the eyebrow is often missing Ordinarily the scalp hair is not only unaffected but seems to be especially well developed If the under-developed gonads start functioning e g after successful treatment with anterior pituitary hormone the body hair and the other secondary sex characteristics may still develop Several authors emphasize the small thin under-developed nails which do not show lunulae at their bases Onychogryphosis fragility of the nails and opaqueness of the nail substance have occasionally been noticed

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[1162] ..rl ghau E. L. F. Jocel Therapy i General Practice Chicago Ill 1940 Year Book Publishers Inc

[1163] Rynearso F H Hormones of the Anterio Lobe of the Pituitary Body J A M A 125 5 1944

[1164] Rowntree F Jocel Diseases a R aled by 13 000 000 Examinations of Registrants J Clin E docri ol 4 515-518 1944

[1165] Cushing H The Pituitary Body and Its Disorders Philadelphia 191

In the rare *Laurence Moon Biedl* syndrome which consists of dystrophia adiposogenitalis retinitis pigmentosa mental deficiency and polydactylism cutaneous peculiarities other than in Frohlich s syndrome have not been recorded

L Frankel noticed the failure of the lateral parts of the escutcheon to develop in patients with *pituitary infantilism* (After Mussio Fournier [16])

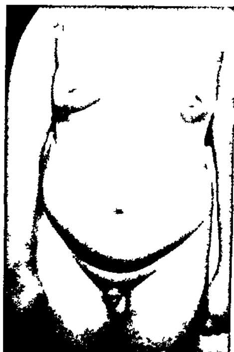


Fig 164 Fröhlich s type Male aged 15 years Obesity gynecomastia lack of pubic hair

The complete absence of secondary sex characteristics dryness of the skin freckles and hypotrichosis of body and scalp is the rule in *dwarfs of pituitary origin* (Type Lorain Levi) The scalp loses some or much of its hair mostly in the vertex area less so at the margins This vertex type of alopecia has been observed in several pituitary conditions (Engelbach) *Cutis laxa* and *Ehlers Danlos syndrome* has in some cases been related to hypopituitarism [15]

Cachexia Pituitaria Simmond's Disease

Simmonds Disease occurs almost exclusively in women after childbirth The cause is atrophy or destruction of the glandular part of the pituitary

The early stages of this syndrome resemble myxedema Later with increasing wasting amenorrhea or in the male impotence develops Muscular weakness extreme loss of fat hypotension apathy and hypersomnia low temperature low blood sugar low basal metabolism and eosinophilia compose a picture which can easily be confused with other cachectic conditions Good and sometimes dramatic results have been obtained with anterior lobe extracts

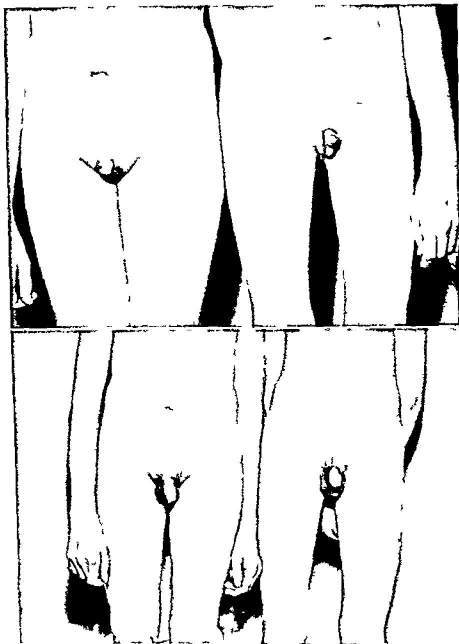


Fig 163 —Brothers aged 24 and 17 years Arrested sexual development at the age of 14 Froehlich type Almost no pubic hair obesity *Below* after one year of treatment with gonadotropic hormone and testosterone (Courtesy Wisconsin General Hospital)



Fig. 166 —Lawrence-Moon-Biedl syndrome Note polydactylism (Courtesy Wisconsin General Hospital)

Dermadromes —The skin is waxy pale or yellowish and slightly edematous Later the turgidity disappears and the skin becomes dry wrinkled and slightly scaly or in some areas especially about the hands and feet glossy chilblain like or even sclerodermatic There is a definite tendency toward pigmentation The pubic and axillary hair as well as the eyebrows and beard disappear completely in the fully developed syndrome[1166-1170] In some instances not a single lanugo hair can be detected on the whole body surface The eyelashes and the scalp hair usually stay The nails and teeth fall out or suffer dystrophic changes[1171]

Acromegaly

Acromegaly is caused by hyperactivity of the eosinophile cells of the anterior pituitary which are responsible for the growth stimulating hormone Eosinophile (acidophile) tumors and eosinophile hyperplasia have often been found

The overgrowth affects the skeleton and other systems Maxillary rather than mandibular prognathism is characteristic of the true acromegalic The nasolabial folds deepen and the ears seem to be set back The teeth become separated and the hands and feet enlarged The viscera take part in the unnatural growth The hyperfunction of the anterior pituitary may be followed by hypo

[1166] B ttinger W Zur K nntnis d Simmonds' h n Krankheit Endokrinologie **14** 369 1934

[1167] Die Simmondssche Krankheit Umfrage M d Kl **32** 8 9 8 93 1387 1936

[1168] Zoltschan J D rmatologische B obachtungen bei Simmonds'ch Leiden Bőrgyógy Szemle **13** 17 1 9 193 Zbl **51** 33

[1169] Costantini F Contributo allo studio della malattia di Simmonds (cachessia ipofisaria) Folia med **38** 1 84 1931

[1170] H mann K Zur Klinik d Simmondsschen Krankheit Münch med Wchnschr **77** 1670 1930

[1171] Grautner W Die hypophysäre Kachexie (Simmondssche Krankheit) Ztsch f klin Med **101** 19 19

function and incomplete regression of the acromegalic signs in the soft tissues[1166] Such a regression in the skeletal system is hardly possible Therefore the typical cutaneous signs of acromegaly may be absent in fully developed skeletal acromegaly

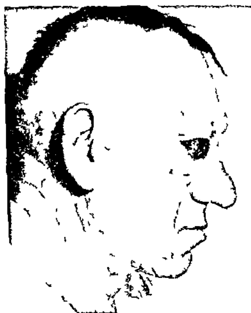


Fig 1C7 —A rom g ly N t fr ckl mall fil om leepen g of furrow e pec ally nuchal a l nas labi l f l l E r s ns to b t back (Courtesy Wisconsin G ne l Ho p tal)

Dermadromes —In acromegaly the skin like the bones and the viscera is overdeveloped in every direction and can be compared to a normal skin under a magnifying glass The surface is coar e the furrows deepened and the connective tissue thickened or somewhat edematous Moles may appear or existing ones grow Combination with Recklinghau en s di ea e has been ob erved a number of times[117] The cutaneous glands are enlarged and their hyperactivity is indicated by moisture and seborrhea Comedos and follicular kerato es are marked Acne is not uncommon The pigmentation is moderately accentuated[1165 11 3] The hairgrowth is increa ed in about one fourth of the cases occurring[1165 11] especially on the body so that in women a more masculine habitus re ults In only even per cent does the hair growth decrease[11 5] By feeding young rat or injecting young dogs with anterior lobe extract the hair has been shown to become thicker than in the control[11 4] (Robertson 1917 after Mu sio

[?] Atkl so F R B A omegaly From a St ly of th Lit ratu 1 31 1934 Fr Jokrinologi 17 3) -3?0 1 36

Atkinso F R B A rom g ly Lo 1 193 Joh Bal o & Danielsson Ltd

[?] B w A W a 1 La n (H tu lies f th En loc in Gland II Th Pituitary F loc ir logy 12 4-3 1 3

[?] D 11 ff L M A rom galy 100 Cases En loc i ol gy 10 461 19 6

[?] Cortsch F Infl f Pituit y Feeding Upon Crowth a 1 S xual D vel pm t Bull Jol s H ki Ho p 27 ?-49 191?

Fournier[15]) Occasionally blond hair becomes darker and straight hair becomes curly and negroid[1177] The scalp hair may become thin on the vertex[1178] and premature greying may be seen The nails participate in the general hyper trophy becoming broad striated sometimes spoon shaped (koilonychia)[15]

Fig 168

Fig 169

Fig 168 Cushing's syndrome Broad purplish striae obesity (Courtesy Wisconsin General Hospital)

Fig 169 Broad purplish striae in Cushing's syndrome (Courtesy Wisconsin General Hospital)

and occasionally long (Walker after Atkinson[1173]) Varicose veins are not un common

Cutis verticis gyrata[1179] is a congenital anomaly consisting of an excess of scalp which causes the skin of the vertex to form folds and furrows resembling

[1177] Aschner B Der Einfluss der Hypophyse auf die weiblichen Geschlechtsorgane Med Klin 20 1681 1685 1924

[1178] F g ll a b W Hair Growth and Pigmentation M Clin North America 9 1 43 1925

[11] Jadassohn J Ein eigentümliche Furchung Erw it ru g u V ll kung 1 Haut am Hi t r kopf 9th Kongr Deutsch dermat Ges Bern 1906

the gyri of the brain This peculiar and rare lesion has been observed more than nine times in acromegaly which is often enough for it to be considered an occasional pituitary dermadrome [1178 1180 1181]

The combination of acromegaly and xanthoma diabeticorum has been reported five times in three years [1179] Persistent edema of the eyelids face and extremities is well known and transitory circumscribed edema of the Quincke type has also been reported [1185]

Basophile Adenoma

Basophile Adenomas produce a characteristic group of symptoms now well known as Cushing s syndrome The neoplasm develops mostly in young adults The highest age in twelve cases recorded by Cushing was 25 years The patients are definitely undersized since they become shorter during the disease The duration of the ailment averages slightly over five years Adiposity is characteristically confined to the face neck and trunk the extremeties being spared The fat deposits are often tender and develop quite rapidly The round face

F[illegible] 1 0 [illegible] Cushing [illegible] syndrome F[illegible]mal ag[illegible] 13 years Am[illegible]o[illegible]rh[illegible]a [illegible] of 13 obesity stria [illegible] Normal [illegible] grou[illegible]d (Courtesy the late Dr [illegible])

[illegible] Akromegali mit Cutis verticis gyrata Hospitalstid [illegible] 781 48

Forest [illegible] Forest [illegible] Cutis Verticis Gyrata With Associated [illegible] Disease Arch Dermat & Syph 29 [illegible] 193[illegible]

[illegible] occipitale verticillée (Cutis verticis gyrata [illegible] rapport [illegible] acromégalie Bull Soc franç d dermat et syph 39 14[illegible]-1435 193[illegible]

[illegible] Hypophyse[illegible]bestrahlung bei Cutis [illegible] gyrata Acta radiol 19 [illegible] 1938

[illegible] Soc Med 25 66 193[illegible]

[illegible] Akromegali und Zwischenhirn Deutsche Ztschr [illegible] 504 146 19[illegible]

is often described as a full moon face but the facial expression is more painful than jolly Weakness kyphosis back aches amenorrhea in the female and impotence in the male are other symptoms

Dermadromes —The most striking dermadrome is the development of broad purplish striae atrophicae mainly in the lower and lateral parts of the abdominal skin They were present in all of Cushing's twelve cases and have since been seen in a great number of instances[1186] It seems as if the basophile adenoma produces a toxic substance with a special affinity to the elastic fibers Their resistance and elasticity appear to be weakened so that they tear on relatively slight strain (see striae of pregnancy)



Fig 171 —Cushing's syndrome Livedo reticularis (Courtesy Wisconsin General Hospital)

The skin is often hyperpigmented[1186] It is dusky or copper colored especially the face It is usually dry Purpura traumatica has frequently been observed

Hypertrichosis of the face and trunk has been constantly found in females and preadolescent males

Many secondary endocrine disturbances are on record such as those due to dysfunction of the thyroid and adrenals Diabetes has been recorded

The resistance against infections is lowered this leads to frequent pyodermas Infections are often the immediate cause of death

[1186] Jonas Cushing's Syndrom Med Klin 1936 I 814

CHAPTER XVII

DISORDERS OF THE ENDOCRINE GLANDS

THE THYROID GLAND

Thyroxin the hormone of the thyroid gland stimulates the oxidative processes of the body

The influence of the thyroid on the skin is manifold [118] The removal of the gland in animals increases the content of water and chlorides the total nitrogen and the protein derivatives in the skin Administration of thyroxin decreases the cutaneous chlorides and the water and increases the sugar and nitrogen Some of these effects may be rever ed with high doses of thyroxin Thyroidectomy increases the capacity of the skin to swell in 1/10 normal HCl (Quellung) Thyroxin causes higher and more prolonged skin and blood sugar tolerance curves The resorption time of a saline wheal is prolonged after thyroidectomy and shortened under the influence of thyroxin while the resorp tion of potassium iodide shows an opposite tendency Thyroxin increases the sensitivity of the skin to X ray and ultraviolet rays [1188]

Hyperthyroidism (Grave's Disease, Basedow's Disease, Thyrotoxicosis, Exophthalmic Goiter)

The skin in hyperthyroidism is smooth thin and elastic with a velvety feel[1189] This is in part a constitutional characteristic and is often present before any symptoms of the disease become apparent The skin is moist warm and rosy but the color is unstable The elevation of the temperature is roughly propor tional to the increase in the metabolic rate The difference in temperature between covered and exposed skin areas is less pronounced than in a person with a normal metabolism It seems that the thinness of the skin as well as the increased temperature and moisture helps to free the body from a surplus of heat created by the elevated metabolism The patients usually complain of exces sive warmth and like to sleep with the limbs uncovered

Dermadromes —Erythema of the chest and back and of the parts where the clothing presses is common [1190] Unexpectedly the capillary microscope shows that the capillaries are thinner than normal[1191] although observations of enlarged

[118] Bohnstedt R M Experimentelle Untersuchungen über die Beziehungen zwischen Haut und inkretorischem System Arch f e p r Path 176 475 1934 1935

[1188] Ellinger F Über die Bedeutung der Schilddrüse für den Ablauf der Strahlenreaktionen an der Haut Klin Wch schr 11 1049 193

[1189] Youman J B Changes in the Skin in Thyrotoxicosis Am J M Sc 181 681-692 1931

[1190] Sloan E P The Thyroid Springfield Ill 193 Charles C Thomas

[1191] Michal M and Buschke W Ueber das Verhalten der Hautcapillaren beim Morbus Basedowii Klin Wch schr 11 1592 1593 1932

capillaries have also been made [1192] Dilatation of the arterioles of the sub papillary plexus accounts for the increased rate of the peripheral blood flow and the high skin temperature (Bansi after Michael and Buschke[1193]) Due to the increased moisture the electric resistance of the skin is low

Hyperhidrosis is often as marked and as weakening as in pulmonary tuberculosis [1190, 1194] Seborrhea acne and comedos indicate overactivity of the sebaceous glands In about 50 per cent of the cases[1195] there exists a tendency to increased *pigmentation* The hyperpigmentation is often inconspicuous this explains the much smaller percentages in some series Youmans[1189] sees a difference from the pigmentation in Addison s disease mainly in its lesser degree and in the lack of pigmentation of the mucous membranes The pigmentation seems to have the older authors more impressed than those of recent years [1194] The hyperpigmentation of the eyelids is often regarded as suggestive of hyperthyroidism (Jellinek s sign)

Vitiligo has been seen in roughly 10 per cent of the cases [1195, 1196] This is high enough to warrant a basal metabolism test in all ca es of vitiligo

There exists a marked tendency to transient *edema* Unexplained puffiness *of the eyelids[1197] and ankles chronic urticaria[1198] and angioneurotic edema should* cause the physician to think of hyperthyroidism The resorption time of intradermally injected saline (McClure Aldrich test) has been found to be prolonged in untreated cases with a return to normal after operation or iodine treatment [1198] The validity of these findings however has been disputed [1199]

Maranon s sign is the more marked and longer lasting red dermographism in the skin covering the thyroid gland as compared with the red dermagraphi m in other areas The sign is frequently positive in hyperthyroidism but is not specific [1200]

The *hair* is very sensitive to the toxic effects of hyperthyroidism Sainton[1201, 1202] and his collaborators noticed diffuse or circumscribed loss of the hair in 43 per cent of their 180 cases The vertex and the temples are especially affected [1201, 1203]

[1192] Robe ts E and Griffith J Q Jr Quantitative Study of Cutaneou Capillarie in Hyp r thyroidism Am Heart J **14** 598-60? 1937

[1193] Micha l M and Buschke W Das Verhalten der Haut apillaren b im Morbus Bas dowii Deutsche med Wchnschr **59** 134 135 1933

[1194] Hyde and McEwen The Dermato es in E ophthalmic Goitre Am J M Sc **125** 1000 1903

[1195] B amwell B Anemia and Diseases of the Blood forming Organs and Ductl Gland 1899

[1196] Hab rmann R Paratypische Pigmentanomalien Ha db d H u Gk **4** 2 706 934 1933

[1197] Dore Cutaneous Affection Occurri g in th Course of Graves Disea e Brit J Dermat **12** 353 1900

[1198] Rouss l J N Chronic Urticaria a Thyro-Adrenal Syn lrome How to D t rmi e th Direction of th Dysfun tion and What Type of Agent to Employ in Its Treatment South M J **22** 668-672 19 9

[1199] Mora J M Intracutaneous Salt Solution Test in Thyrotoxico is Am J M Sc **177** 219 19 9

[1200] Efrousi Ryss R Le signe d Marañon t a signification dans l goitre exophtalmique Thè de Pari 19 6

[1201] Sainton P and Simonn t H Les troubles de la fonction thyroïdienne et l ur action sur le système pil ux A n de méd **29** 263 0 1931

[1202] Sainton P and Mamou H *Hyperthyroidi me provoqué par la thyroxine ynthétiqu* chez un malade att int d un syndrom pluriglandulair a ec sclérod rmi et cataract Bull et mém Soc méd d hôp de Pari **43** 1685 1927

[1203] Foerster O H The R lation of Inter al Sec tions to Cutaneous Disease J Cutan Di **34** 1 1916

Typical *alopecia areata* is not infrequently associated with hyperthyroidism an observation already made by Basedow [1 04 1 05] Alopecia as well as canities may affect the head hair the beard the eye lashes the eyebrows and the body hair Some authors emphasize the frequency of alopecia of the lateral third of the eyebrows White spots in the hair have often been recorded [1206] Improvement of the hyperthyroid condition may be followed by improvement of the alopecia Universal baldness as well as hypertrichosis are rare [1207]

Alopecia as well as canities has been experimentally produced in animals by feeding with human or animal thyroid or with thyroxin [1 08 1 09]

Melanization however has also been observed after thyroid feeding [1 10 1 11] Chickens are much better fit for these experiments than cats and rabbits [1 1] The sudden production of alopecia and canities after mental shock and terrifying experiences which so far has not been well substantiated could be explained by sympathetic stimulation of the thyroid [1 13 1 15]

In thyroidectomized rabbits regeneration of plucked hair is delayed or absent [1 16 1 17] Thyroid extract feeding speeds the regeneration of plucked feathers in pigeons [1 18]

There is no relation between the severity of the hair changes and the severity of the hyperthyroidism This refers to the clinical observations as well as to the animal experiments The blood of thyroidectomized horses compensates the effect of thyroid feeding on the integuments [1 19] The extract of toxic goiter is reported to be more effective on the plumage of chickens than the extract of simple goiter [1 19]

In spite of these and other suggestive experiments the etiology of *alopecia areata* has not been elucidated It seems that many factors are able to produce

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[1 04] Von Basedow G A Exophtalmus lurch Hypert phie des Zellgewebes in der Aug nh?hl Wchnschr f d ges H ilk Be lin 1840

[1 05] Sabouraud R Diagno ti et traiteme t des affections du cul chev lu Paris 103? Masson t Ci

[1 06] P yn t J Dy trophies et dyschromies des fo mati s épid rmiques au ours du synd ome de Basedow (M lanod rmi exceptée) Th e le Paris 19 6

[1 07] S h resch w ky N N D l infl ence des s crétions ndocriniennes sur la pouss des poil R v franç d Endocrinol 3 301-31 19 5

[1208] Zavadovski Effect of Single Doses of Thyroid Gland on Fowls Endocrinology 9 1?5 136 ?3 241 19 5

[1 09] Za adov ki B M Hormo e und da Gefieder d r Vögel Endokri ologi 10 3 36 1932

[1 1] Col and P ld M lani ation Aft r Thyroid Feeding J Agricult Research 22 10-4

[1 11] Cr w and Huxl y Melanization of Chicken Feath rs Aft r Thyroid Feeding V t J No 9 19

[1 1] Sainton P Ma imin M and Mamou H L hyperthyroïdisme t son acti n sur les phanères Bull Soc franç d d m t et yph 35 ?? ?7 19 S

[1 1] Lévy F kel A a l Ju ter F Pech rch ur l mécanisme phy iopathologique de la pelade II P lades traum tiques t pelades p choc émotif Ann. de dermat t syph 2 1074 1088 1931

[1 1] Ram l Postt aumatische Alopeci areata Zbl 44 5 5 1933

[1 15] Ba be H W I ost Traumatic Alopeci Areata Proc Roy Soc Med 25 9?5-9?6 1932

[1 1] Furuya K B lt äge ur Physiologi d r Drüsen Wa hstum der Haa e und Schil l ird Biochem Ztschr 137 4 5 19 4

[1 1] Cooper Z K Endocri e Glands and Hair Review of Literatu e A ch D rmat & Syph 21 1007 10?9 1930

[1 1] Lari nov W Th Woitkewitsch A A and B l ky N W Di R g n ration des Gefieders d r T uben bei v rschied nen humoral n Einwirkungen E dokrinologi 12 416-4 ? 1933

[1 1] Sainto P H Simmo et a d Barbé P Action comparée des extraits de gland thyroide de basedowi ns et d goitreux sur le plumage des gallinacée Bull Soc fra ç de dermat et yph 37 684 686 1930

the same typical picture which is more than twice as common in men as in women[1 0] Infection[1 1 127] seems plausible in a number of cases Hyperthyroidism as well as hypothyroidism[12 3] has been seen too often in alopecia areata to be dismissed as a coincidental occurrence[1 3 1 6]

Fig 172





Fig 173

Fig 17 —Alopecia totalis Mod rate hypothyroi li m
Fig 173—Sam patient after treatm nt with thyroid

1270 Waisman M and Kepler E J Alopecia Areata An Appraisal of Endocrine Factors in Its Causation J A M A 116 2004 2006 1941

1271 Cederberg A Unt rsu hungen über die Alopecia areata mit besond r r Berücksichtigung ihr r Aetiologi Zugl i h ein B itrag ur Vitiligog nese Duodecim 47 83-853 1931 Zl I 40 334

1272 pitz r R Zur A tiologi und Symptomatologie d r Alopecia areata Arch f Dermat u Syph 132 268 1929

1273 Throne B Basal M tabolism in D rmatological Con litio s New York Stat J Med 30 50-265 1930

127 Ribová V Zur Pathog nese d r Al pecia areata Ceská d rmat 12 55-78 96 102 107 1 9 135-141 193 Zl I 42 435

1275 Bo njakovic Alopecia areata multilocularis Zl I 39 142 1931 1932

1276 Merenl n ler Alopecia a ata mit bed ut nd n Pigm ntstörung n Zl I 41 343 193 1933

Waisman and Kepler[1090] found a metabolic rate of less than minus 10 per cent in 25 per cent of their cases

The occasionally striking success of thyroid medication supports to some extent the thyroid etiology of some cases[15] though the general stimulating effect of thyroid preparations has to be taken into account A pituitary etiology has been claimed on the grounds of (1) supposed roentgenological changes in the sella turcica[1 8 1 7] which was not confirmed by Waisman and Kepler[1 0] (2) coincidence with pituitary symptoms and (3) successful treatment with anterior lobe extracts[1098 1231] and radiation of the pituitary[6 1 32] There are some cases with ovarian testicular and adrenal findings in alopecia areata with corresponding hormone therapeutic results There are other arguments in favor of a pituitary etiology Vitiligo or chloasma was present in about 10 per cent of Waisman and Kepler's[1 0] series The influence of mental strain and shock is important Preceding infections have also been accused

The *nails* have occasionally been found altered in hyperthyroidism Longitudinal and transverse grooves atrophy onycholysis and leukonychia have been de cribed

Hypothyroidism

However different the symptomatology of congenital and acquired thyroid deficiency may appear there is little difference in the dermadromes of both types The dermadromes of hypothyroidism appear early and therefore they deserve particular attention[1 33 1 34] It is necessary to emphasize that the fully developed syndrome is rare while cases having some of the symptoms occur quite frequently Severe deficiencies of the thyroid have been observed with or without skin changes

In hypothyroidism the skin is pale and often slightly yellowish due to carotenemia[15 1235 1 36] It seems that the liver is unable to form Vitamin A from carotene due to the lowered metabolism The skin is cool to the touch and the patient feels the cold more intensely than normal persons The coolness of the skin is considered to be one of the earliest symptoms in the whole syndrome of hypothyroidism The lowered temperature is especially noticeable in the ex

[1227] Fll r Alopecia Totali and Folli ulitis Arch Derm t & Syph 20 40 19 9

[1228] Tsukad S Ueb r a ffall nd n H il rfolg des Hypophysenv rderlappe hormons geg n Al pecia Jap J D rm t pp 338-339 1933 Zbl 45 19 1933

[1229] B ngtso B S Anteri r Pituita y Therapy in Alopecia Totalis Clin Med & Surg 40 591 594 1933

[1230] T ukada S an I Akal hi K W it re E fahru g n au d r Hormonth rapi der Alopecia areata n bst hämatologisch r klorh misch n I neurologisch r Unt rsuchung Jap J De m & Urol 34 1933

[1231] Whit A W Pituita y E tract i the T eatm nt of Alopecia Canad M A J 31 301 1934

[1232] Urbach E E folgr ich ätiologisch Therapi bei en lokrin bedingtem Haarau fall Zbl 35 310 1930

[123] Pel nko A Chroni In uffi i ncy of th Thyroi l Cla d Rusk Vest D rmat 5 Nrs 4 10 19 Zbl 28 160

[2] K na Apal l hti L Wirkung I r Thyreoidinbehandlung auf di H ut les Myxödemkindes Histologische Unt rsuchung n A ta Soc med Duodecim 15 2 1 13 1931 Zbl 40 630 1932

[123] Escamilla R F Caroti mia i Myxed ma Explanation of Slightly Icte ic Tint J Clin E locrinol 2 33-3 193

[1236] Mand lbaum T Caudel S a I Millman S Hypothyroi lism Hyperlipemia and Carotenemia J Clin E docrinol 2 465-467 194

tremities where it is sometimes combined with acrocyanosis and associated com plications like chilblains and tuberculids[1237] Several authors[1238, 1239] saw deep ulcerations of the legs connected with hypothyroidism and they advised treat ment with thyroid by mouth and thyroid powder or thyroid salve locally The skin is dry especially on the extensor surfaces of the extremities In some cases of acquired myxedema marked keratosis palmaris and plantaris was observed and successfully treated with daily doses of 0 2 — 0 3 Gm of thyroid[15 1 33 1240 1241] The basal metabolism has often been studied in congenital ichthyosis The findings and the results of thyroid therapy are controversial[1 4- 1 44]

The dryness of the palms and arm pits (anhidrosis) is striking since the secretion of the sweat glands and of the sebaceous glands is reduced or completely absent Nevi and moles may appear and desquamation is pronounced due to the dryness and to the tendency toward increa ed keratosis In advanced or neglected cases this may cause a picture similar to ichthyosis particularly around the knees and elbows and also in the axillary and inguinal folds (Reuter in dis cussion to Cornbleet and Cohen[1245]) In some ca es of congenital ichthyosis thy roid therapy seems to have given relief[1246 1248] Itching is a frequent complaint

The edema in fully developed myxedema is nonpitting and firm It is most marked in the face and in the ears which sometimes have a cauliflower like appearance[1190] The facial features are coarse The term eskimo face[1249] is significant Eyes and nose appear smaller than normal the latter especially in children is saddle shaped This sign is commonly met with The eyelids especially the lower lids the skin of the forehead the ears and the lips are swollen and cause a deepening of the nasolabial and forehead folds The supraclavicular fossae and the dorsa of the hands and feet are other sites of increased myxedem atous or fat pads The swelling may extend to the mucosae The tongue the uvula and the nasal and laryngeal mucosae may become involved with a con sequent disturbance of the voice The thick protruding tongue of the cretin is a familiar picture

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[1237] Covisa and B Janaro Tuberkulide and Hypothyr oidismus Actas d rmo-sif **13** 4 1921 Zbl **3** 353

[1238] Coh n M H Leg Ulc rs Due to Thyroid Dysfunction J A M A **102** 283 285 1934

[1239] Eppinger H Torpide Hautgeschwü e als Symptom ines lokalen My ödem Kli Wchnschr **10** 682 683 1931

[1240] Mussio Fourni r J C Kératodermie plantair et palmaire ch une hypothyroidi n e Sa guéri on par la thyroidin Bull et mém Soc méd d Hôp d Paris **48** 1236 1237 1932

[1241] Cervino J M Vertoll i A and Larro a H Igu ra R A Keratod rmia of Hand and Feet and Thyroid D fici ncy Endocrinology **22** 615 1938

[1242] Krogh M and With G On the Standard M tabolism in I hthyosis Acta I rmat v ereol **3** 558 19 2 Zbl **9** 50

[1243] Si m ns H W Unt rsuchung n über d Stoffwechs l Ichthyotisch Arch f D rmat & Syph **149** 466–476 1925

[1244] Porter A Basal Metaboli m i Ichthyosis Brit J D rmat **38** 475-491 1926

[1245] Cornbleet Th and Cohen D Pellagra and My edema Arch Dermat & Syph **42** 1140 1940

[1246] Sieben H I hthyosis als Folge en lokri r Störung D rmat Wchnschr **91** 710-712 193

[1247] Deusch G and Neuhaus C Myxöd m und Ichtyosi Münch n med Wch schr **76** 1561 1929

[1248] I i nou S Ichthyosis simplex Jap J D mat & Urol **36** 107 1934

[1249] P trac k F Ein Fall von chronischer Insuffizi nz d r Thyreoi lea Ein B itrag zur Pathologie des Öd ms Česká d rmat **12** 233 241 1931 Zbl **39** 72

Increased pigmentation especially on the forehead around the lids and some distance from the mouth occurs Severe bronze colored pigmentation of the body has been observed in cachexia thyreopriva [1251] However it is doubtful whether or not the pigmentary changes are caused by the hypothyroidism Curschmann[1 5] infrequently found grey hair in adult patients He relates this finding to his observation that adult patients with chronic myxedema due to their lowered metabolism age later than normal persons This author found patients with compensated myxedema at the age of sixty and seventy years look like forty five Other authors frequently found premature greyness in myxedema [15]

Loss of hair is common in hypothyroidism This clinical observation is supported by observations on thyroidectomized animals The hair in myxedematous patients is dull dry brittle and easily wears off and sheds The axillary and pubic hair becomes scanty or absent [15] The margins of the scalp tend to become bald Bald spots not always of the common areata type occur and may respond well to thyroid therapy although this treatment is ineffective in the majority of the cases of alopecia areata In women baldness of the fore head is sometimes striking

The significance of the loss of hair of the lateral third of the eyebrows as a symptom of hypothyroidism especially in children (Hertoghe s or Levy and Rothschild s sign) is not generally recognized It is less pronounced in the Teutonic races with whom thinner eyebrows are considered normal

In some cases of hypothyroid infantilism the lanugo hair persists in considerable strength but disappears with thyroid medication [15]

The *nails* are often changed Dystrophies have been found in some series up to 93 per cent [1253] The size can be decreased the normal curvature absent and the nail may be very thin Decrease in size brittleness longitudinal and transverse grooving defective lunulae and white spots in the matrix are common [1 50] The rate of growth is markedly reduced [1233]

The resistance to pyogenic infections blepharitis and erysipelas is low in myxedematous patients The clinical appearance of the myxedematous skin is the result of edema and excess mucin in the epidermis degeneration of the collagen and elastic fibers and a sparse cellular infiltration about the vessels [1 54] The electric resistance of the myxedematous skin is increased [15 1 17]

Circumscribed Myxedema

This not extremely rare condition is a paradoxical one (Trotter in disc to Freudenthal[1 55]) It consists of pretibial circumscribed lesions which are

[1] Koch r A Di Pathol gi d r Schilddrü XXIII Congr inn Med Wiesbaden pp 59 137 1906

[125] Curschmann H Zur Klinik und Pathophysiologie des Myxoedem (in besond re der gutartigen I k mpl (t n Fo me) D utsche Ztschr f N rvenh 98 1 8 19 7

[1 5] Barrett A M H reditary Occurrenc of Hypothyroidi m With Dystrophies of the N ils and Hai Arch Neurol & P ychiat 2 6 8 1919

[1 54] R uter M J Hi topathology of th Skin in Myxed ma Arch D rmat & Syph 24 55 1931

[1255] Freu lenthal W and B linauer St R Myxoed ma papulosum et an ulare Proc Roy Soc Med 35 388-390 194

myxedematous in appearance and histology but are in the majority of the cases associated with hyperthyroidism even with the fully developed syndrome of exophthalmic goiter It seems as if in these cases some parts of the skin especially of the lower legs are unable to use the hormone which is offered in abundance



Fig 174



Fig 175

Fig 174 —Circumscribed tuberous myxedema (Courtesy Division of Dermatology Department of Medicine University of Chicago)
Fig 175 Myxedema tuberosum (Courtesy Dr M J ner)

The lesions are hard nodules or tuberous plaques of varying size sometimes covering both pretibial areas They are symmetrical and may be normal in color yellowish pinkish or brownish Inflammatory symptoms are mostly absent The follicles are often dilated so that a pig skin or orange peel appearance results The lesions are quite hard and nonpitting Hypertrichosis within the lesion is another paradoxical feature which has been encountered [1256] The sweat secretion within the myxedematous lesions is normal or absent [1257] The tempera

[1256] Ri ht r W Lokales My e m mit Hyp ri tosis sym t isch a bei l Unt rsch nk in bei kra k r mit B low 71 42 5 1 193

[1257] Ingram J T Circumscribed Myxedema Associated With Hyperthyroidism R v méd Latino am 18 1 3-131 193 71 41 56 1933

ture may be much lower than in the normal skin[158] On puncture a mucilaginous tenacious serum seeps from the wound The microscope shows infiltration with masses and strands of mucin

The major changes are found in the cutis The connective tissue fibers are edematous and homogenized Oval and stellate cells are scattered throughout[158,159,160] Treatment with thyroid or iodine has occasionally produced toxic symptoms Thyroidectomy precipitated the outbreak of circumscribed myxedema in some cases but abolished it in others Since this dermatosis causes little discomfort the treatment should be guided by the necessities of the general condition[161]

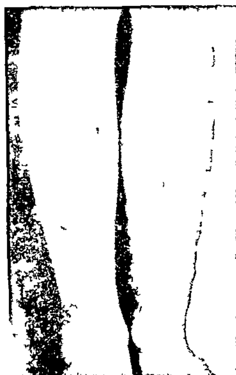


Fig 1 6 —Myxed ma tub ro um i i a pati t with hyp thyroidism From Am rstach J O Arch D rmat & Syph 1944)

Lichenoid umbilicated papular[158] tuberous plaque like and other varieties of discrete myxedema are known as the atypical myxedema of Jadassohn and Doessekker[1] The connection with thyroid dysfunction is usually less obvious

[158] Carol W L L Atypisches My od m Ned l Tijdschr v ge eesk 75 4156-4169 1931 Zbl 39 78

O Lea y P A Lor il l l Ed ma f th Extremiti s in Association With E phthalmic C iter Arch D mat & Syph 21 5 0 193)

[160] O Lea y P A l l F l ma of th Fa Arch D mat & yph 21 330-331 1930

[1] Hal e S F E pt th lmi C lt an l My l ma En locrinology 12 19 8

[1] D essekker W Atypisches tuberoses Myxoed Arch f D mat u yph 123 76 1916

in this group than in diffuse or pretibial myxedema[1255] The oral mucosa may be involved[1 6]

Temporary facial puffiness following subtotal thyroidectomy but different from the localized form of myxedema has been observed in nine cases[1263] It seems to be a mild form of myxedema and responds to thyroid therapy

The Parathyroid Glands

The hormone of the parathyroid glands is concerned with calcium metabolism It maintains the level of ionized calcium in the blood and regulates the use of calcium for skeletal growth The proper degree of nervous and muscular irritability and the viscosity and coagulation of the blood are also influenced by the pre ence of calcium

Relations between the parathyroids and certain dermatoses have often been suspected (see scleroderma calcinosis) but our knowledge of the skin in hyperparathyroidism is meager and uncertain Albright[1264] in his work on hyperparathyroidism does not mention any skin changes and no mention is made in the review of 135 proven cases by Wilder and Howell[1265]

Hypoparathyroidism

Extirpation of the parathyroids was in a number of cases followed by the outbreak of a evere and characteristic dermatosis clinically identical with impetigo herpetiformis (Hebra) Since other symptoms of insufficient parathyroid activity especially tetany have been found in spontaneous cases of impetigo herpetiformis it seems justified to regard this disease as a dermadrome of hypoparathyroidism

Impetigo Herpetiformis—Hebra[1266] in 1872 and shortly after him Kaposi[1267] first described the clinical picture of this disease and it has been but little changed since The dermatosis starts with crops of pustules which often appear during pregnancy but sometimes in women without relation to pregnancy or in men The primary lesion is a true pustule i e a vesicle filled with pus from the beginning and has a red and swollen base These pustules are the size of a pinhead and are superficially seated in the epidermis being grouped in clusters and lines Confluent pustules in the center of such groups form a scab (impetigo) while new pustules develop at the periphery and the center heals under the scab forming rings and polycyclic figures

These eruptions may cover large areas sometimes the whole body surface The navel the genital and inguinal areas the armpits and the submammary

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[1263] Thompson a d Thompson Tempora y Ed ma of the Face Following Tr atm nt for Exophthalmi Goit r Am J M Sc 178 73 1929

[1264] Albright F Aub J C and Bau r W Hyperparathyroidi m J A M A 102 1276 1 87 1934

[1265] Wilder R M and How ll L P Etiology and Diagnosis in Hyperparathyroidi m A Revi w of 135 Proved Cases J A M A 106 427-431 1936

[1266] Hebra F Ueber einig in d r Schwang rschaft und bei Uterinalkrankh it n l r Frau beobachtete Hautkrankh iten Wi n med Wchnschr 187

[1267] Kaposi M Impetigo h rpetiformis Arch f Dermat & Syph 19 273 36 1887

regions are usually first and most severely involved Deep ulceration has not been seen Sometimes the mucosa shows lesions analagous to those of the skin Crops of new pustules are often accompanied by chills and fever Nephritis splenomegaly and cachexia are the rule in fully developed cases which may take on the aspect of generalized exfoliative dermatitis Itching is not a dominant symptom

Impetigo herpetiformis is a severe and often fatal disease Of the thirteen patients with impetigo herpetiformis reported by Kaposi[1 67] from 1872 to 1884 twelve died from the disease Glavecke[1 69] (1896) found a mortality of 80 per cent among 20 cases from the literature During the last twenty years relatively many nonfatal ca es have been reported

This disease is so rare that many dermatologists have never seen it The great interest which it aroused is due to the fact that it is a characteristic dermatosis with a definite endocrine relation hip Hebra[1266] and Kaposi[1 67] who saw more cases than any other writers were convinced that impetigo herpetiformis is a disease of pregnant women Later on Kaposi described a case in a man and more recently several cases in nonpregnant women in children and in men[1 69] have been presented

In 1921 Schardorn[1270] reported two cases of impetigo herpetiformis and tetany in nonpregnant women who only three days before had been subjected to thyroidectomy Both women died and at autopsy no parathyroids were found If there was any doubt about the part the operation played in the etiology it has been removed by the publication of at least nine more cases following thyroidectomy [1271 1278] In a case published by Kolisch [1279] tetany followed thyroidectomy The patient later became pregnant and developed impetigo herpetiformis On the other hand it is surprising that impetigo herpetiformis has not been een more often among the many cases of total thyroidectomy Kocher [1 51] e g in his famous paper in 1906 does not mention impetigo herpetiformis as a symptom of cachexia following total strumectomy

The spontaneous cases in pregnancy are often but not always associated with symptoms of hypoparathyroidism Osteomalacia tetany [1 78 1280 1281] low

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[1268] Gläveck Impetigo herpetiform Arch f Gyna k 52 18 34 1896

[1269] Hall A F Impetigo h rp tiformis I Mal Arch D mat & Syph 50 10 11? 1944

[1270] Schard rn Impetigo h petiformi Arch f Dermat u Syph 132 109-1 0 19 1

[1271] Lutz Impetig he p tiformis D rmat Zt ch 63 384-390 19 8

[1272] Lapp D rmatitis parathyreopriva unt dem Bild der Imp tigo herp tifo mis Zbl 39 13 1931

[1273] Bartmann J Zu ätiologisch Th r pie der Impetigo h petiformis Arch f D rmat & Syph 175 93 106 1937

[1274] Wi F D matiti herpetif rmis Appearing Three Week After Thyroidectomy A ch D rmat & Syph 27 537 38 1933

[1275] Schmitt Lalia m Impetigo He petifo mi and Cu With A T 10 (Dihydrotachy terin H lt) Med Klin 33 1590 1937

[1276] Schubert M Impetigo H rpetifo mi A T 10 Th r pie D mat Wchnschr 102 761 1936

[1277] Danisch F Impetigo h petifo mis postoperativ Tetanie n parathyreoprive Kach xi Frankfurt Ztschr f Path 28 290 19 8

[1278] W rth ma n A Le Impetigo h petiformi Hebra Arch f D rm t u Syph 157 214 33 19 9

[1279] Kolisch F Impetigo h rpetiformi Zbl f Gyn 48 No 9

[1280] Papf rer U ber Impetigo h rpetif rmis und Schwa g rschaft Zbl 11 319 19 4

[1281] Lesz ynski Impetigo herpetiformis Zbl 45 5 9 1933

serum calcium[1283, 1283] and cataract[1278] have been observed with impetigo herpetiformis in pregnancy but a considerable number of cases have been found free of all such symptoms This together with the nonobligatory occurrence after parathyroidectomy suggests that hypoparathyroidism is only one of the pathogenetic factors In which direction other factors may be sought is indicated by cases with pituitary findings[1284, 1285] mediastinal tumor[1286] and dysfunction of the ovaries[1275] The possibility of an infection which only develops under certain circumstances cannot be denied though the lesions and the blood have almost always been found sterile Italian authors have lately suggested a virus infection

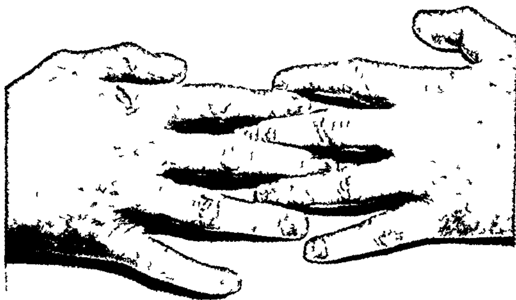


Fig 177 Female aged 1 years Chronic infection of all hand f t and tongu with *Monilia albicans* in a case of tetany bilateral cataract and hyp rte i k n (Courtesy Wilson in Gen ral Hospital)

under certain hormonal and toxic conditions[1287] The clinical similarity to *pustular psoriasis must be mentioned since* hypocalcemia seems to be an etiological factor in this dermatosis also

The *impetigo herpetiformis* of pregnancy brings up the question of the artificial termination of the pregnancy in the case of this disease Several dermatologists feel that this procedure is justified However the disease not infre

[1282]Carter R and I arse R I Impetigo Herpetiform Occurring During Pregnancy Am J *Obst & Gynec* 33 114 1937

[1283]Koch A C Hypocalcinosis Arch f Dermat u Syph 179 33 35 1939 1940

[1284]Tryb A Beitrag zur Aetiologie der Impetigo herpetiformis Arch f Dermat u Syph 172 407-411 1935

[1285]Buschke A Impetigo herpetiformis 71 25 14 1918

[1286]Buschke A Impetigo herpetiformis als Hautaffektion bei Mediastinaltumor Dermat Wchnschr 78 633-635 1924

[1287]Zocchi S Impetigo erpetiformis in gravidanza Ginecologia 8 40 1932

quently starts in the later months of pregnancy when inducing labor in the presence of a widespread purulent skin infection is a dangerous procedure More over the termination of pregnancy does not always influence the course favorably In some cases the patients died from the dermatosis during the puerperium Nevertheless if the diagnosis is made early the pregnancy should be terminated and future pregnancies prevented[1 8 1 88]

There have been almost as many methods of treatment tried as cases recorded Blood transfusions[1289] injections of normal serum and of serum of normal pregnant women[1 90 1 91] estrogenic hormone (Buschke) and X ray sterilization[1 9] have been used Sulfanilamide accomplished a spectacular recovery in one recent case[1 93] Calcium in large doses[1 81] should always be given In tetany Sevringhaus[116] advises the oral administration of a 35 per cent solution of calcium chloride in a sweet vehicle one to two teaspoonfuls three times daily The medicine is given one half hour before meals with plenty of water Parathyroid extracts are unreliable Dihydrotachysterol[1 94] a derivative of ergosterol also known as A T 10 is more promising There are a number of favorable reports on record[1 3 1 75 1276 1 93 1295] The dose is five to twenty drops of the oily solution daily[116] A T 10 is so far the best substitute for the parathyroid hormone It increases the phosphorus excretion and raises the calcium level of the blood

Parathyroid insufficiency seems to increase the susceptibility to *chronic monilia infections* of the hands and nails[1296]

Brittleness of the nails and hairs together with hyperhidrosis and Addisonoid hyperpigmentation is occasionally associated with hypoparathyroidism[15 1217]

The Thymus

Status thymicolymphaticus of the adult is a much disputed condition The beard and body hair has been described as scanty and there often is a female configuration in men[129] Scantiness of the beard and of the axillary and pubic hair in both sexes with heterosexual distribution is part of Timme s syndrome which is a chronic multiglandular benign condition with pituitary gigantism low blood pressure low blood sugar and other features[1298]

[1289] Buschk A and Curth W Di Bed utung d r Cravidität d matos n für Ii künstliche Unt brechung t r S hw g rschaft Mü h n med Weh chr 78 361-364 19 9

[1290] Sch rhe G Zu Beha dlung d r Impetigo he petiformis der v rs hieden n Pemphigusform n unl g wi sch r fl be haft r multiform r Eryth m Bluttran f ion in d r D rmatologie Wi n m l Weh schr 80 717 770 760- 6 801 09 1930

[1291] Rot es Impetigo h p tif rmis Zbl 35 349

[1292] R t es I L Zw i Fäll on Imp tigo he petifo mis D rmat W hnschr 91 1059 1063 1930

[1293] Grütz Impetig h petif mi Zbl 36 710

[1294] Fra k L J Impetigo H petif rmis Arch D rmat & Syph 40 253 5 1939

[1295] Holtz F N ben childdrü ninsuffi i n D utsch med Wchnschr 65 750-6 1939

[1296] h rhe G Zu Klinik t A tiologie t r Impetigo herpetiformi Wi n med Wchnschr 86 1 15 1936

[1297] Sutphin A Albright F and McCu e D J Fiv Cases (Th ee in Siblings) of Idiopathic Hypoparathyroidism Associat d With Moniliasis J Clin F docrinol 3 625-634 1943

[1298] Em rson H Statu Lymphati u in Adults Arch I t Med 13 169 1914

[1299] W lf W Endocri ology i Mod rn Practice Philad lphia 1936 W B Saunders Company

Carcinoma of the thymus has been seen to produce Cushing s syndrome in at least 3 cases [1 99 1301] The juvenile Hercules syndrome of precocious puberty in the male was seen in a case of mediastinal tumor probably a thymus lesion [130] Most thymomas do not provoke dermadromes

Deficiency of the thymus has by several authors been thought to be a cause of *psoriasis* The hypothesis was ba ed on therapeutic results with injections of thymus extract[1303] and stimulating doses of roentgen radiation directed to the upper sternal region [1304 1305] Little has been heard of the subject during the last fifteen years

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[1299]Leyton O Turnbull H M and Bratton A B Primary Cancer of the Thymus With Pluri glandular Disturbance J Path & Bact **34** 635 1931

[1300]Dugnid J B and Kennedy A M Oat-cell Tumors of Mediastinal Gla ds J Path & Bact **33** 93 1930

[130] Thompson K W and Ei nhardt L Cushing Syndrome J Clin Endocrinol **3** 44 -4 1943

[131] Weber E P and Wohl M Macrogenitosomia of Juvenil Hercules Type With Tumor in Sup rior Mediastinum M Pre s **211** ?? 26 1944

[1303]Samberger J Ueber das Wesen der Psoriasis Acta dermat vener ol **2** 359 19 1

[1304]Brock W Beziehungen der inneren Sekretion zur Schuppenflecht und der n Behandlung mit Thymusbestrahlung Strahl ntherapie **11** 5?3 ?04 19 0

[1 5]Brock W *Psoria is und In e e Secretion Deut che med Wchnschr* **47** 1420 14 2 19 1

CHAPTER XVIII

DISORDERS OF THE ENDOCRINE GLANDS

THE ADRENAL GLANDS

The adrenal cortex through its hormone cortin is concerned with water, mineral and carbohydrate metabolism.[1306] It keeps up the muscular strength and it has important functions in pregnancy and lactation. Androgenic substances which are able to masculinize the appearance of females are produced in the adrenal cortex or in its neoplasmas. The medulla of the adrenal glands produces adrenalin which besides other effects stimulates the sympathetic system and inhibits the vagus. Destruction of the adrenals is fatal.

Addison's Disease

Addison's disease[1307] starts insidiously, usually in middle life. Progressive asthenia and muscular fatigability, hypotension, epigastric pain, anorexia, morning sickness and other gastrointestinal symptoms may after long periods of relative mildness suddenly increase and give rise to an acute condition known as Addisonian crisis. Hyperpigmentation of the skin is an outstanding symptom. Dehydration, decrease in the sodium and chlorine concentration in the blood, increase in the blood potassium and nonprotein nitrogen (urea) and hypoglycemia are important findings especially during the crisis. The urinary sodium chloride is high. Sugar may occur in the urine in spite of the hypoglycemia.[1298] The blood viscosity is high. Anemia is marked. The elimination of water after a sudden large intake of water is delayed. A water test designed by Robinson, Power and Kepler[1308] together with blood and urine chemistry has lately been shown to be of great diagnostic value.[1309] The course is almost always fatal but with modern treatment health may be restored to such a large measure that cure may seem to be accomplished, yet sudden death may occur from trivial causes.[1310] The cause of the syndrome is destruction of the adrenal cortex due in 9 out of 10 cases to tuberculosis.

[1306] Goldzieher, M. A.: The Adrenal Glands in Health and Disease. Philadelphia, 1944, F. A. Davis Company.

[1307] Addison, T.: A Collection of the Published Writings of the Late Thomas Addison on the Constitutional and Local Effects of Disease of the Suprarenal Capsules. New Sydenham Society, 1868. Reprinted in Rowntree and Snell: Addison's Disease. Philadelphia, 1931, W. B. Saunders Company.

[1308] Robinson, F. J., Power, M. H., and Kepler, E. J.: Addison's Disease—Diagnosis. Proc. Staff Meet. Mayo Clin. 16: 7-83, 1941.

[1309] Cutler, H. H., Power, M. H., and Wilder, R. M.: Concentrations of Chloride, Sodium and Potassium in Urine and Blood: Their Diagnostic Significance in Addison's Disease. J. A. M. A. 111: 117-122, 1938.

[1310] Rowntree, L. G.: Report of 3 Cases of Clinical Addison's Disease Surviving More Than 15 Years. Endocrinology 26: 793-800, 1940.

Carcinoma of the thymus has been seen to produce Cushing's syndrome in at least 3 cases [1299, 1301] The juvenile Hercules syndrome of precocious puberty in the male was seen in a case of mediastinal tumor probably a thymus lesion [1302] Most thymomas do not provoke dermadromes

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[1299] Layton O Turnbull H M and Bratton A B Primary Cancer of the Thymus With Pluri glandular Disturbance J Path & Bact **34** 635 1931

[1300] Dugnid J B and Kennedy A M Oat-cell Tumors of Mediastinal Glands J Path & Bact **33** 93 1930

[1301] Thompson K W and Eisenhardt L Cushing Syndrome J Clin Endocrinol **3** 445-4 1943

[1302] Weber E P and Wohl M Macrogenitosomia of Juvenile Hercules Type With Tumor in Superior Mediastinum M Press **211** 96 1944

[1303] Samberger J Ueber das Wesen der Psoriasis Acta dermat venereol **2** 3 9 1921

[1304] Brock W Beziehungen der inneren Sekretion zur Schuppenflechte und deren Behandlung mit Thymusbestrahlung Strahlentherapie **11** 563-604 1920

[1305] Brock W Psoriasis und innere Secretion Deutsch med Wchnschr **47** 14 0 14 ? 19 1

Chapter XVIII

DISORDERS OF THE ENDOCRINE GLANDS

THE ADRENAL GLANDS

The adrenal cortex through its hormone cortin is concerned with water mineral and carbohydrate metabolism [1306] It keeps up the muscular strength and it has important functions in *pregnancy and lactation* *Androgenic substances* which are able to masculinize the appearance of females are produced in the adrenal cortex or in its neoplasmas The medulla of the adrenal glands produces adrenalin which besides other effects stimulates the sympathetic system and inhibits the vagus Destruction of the adrenals is fatal

Addison s Disease

Addison s disease[1307] starts insidiously usually in middle life Progressive asthenia and muscular fatigability hypotension epigastric pain anorexia morning sickness and other gastrointestinal symptoms may after long periods of relative mildness suddenly increase and give rise to an acute condition known as Addisonian crisis Hyperpigmentation of the skin is an outstanding symptom Dehydration decrease in the sodium and chlorine concentration in the blood increase in the blood potassium and nonprotein nitrogen (urea) and hypoglycemia are important findings especially during the crisis The urinary sodium chloride is high Sugar may occur in the urine in spite of the hypoglycemia [1308] The blood viscosity is high Anemia is marked The elimination of water after a sudden large intake of water is delayed A water test designed by Robinson, Power and Kepler [1309] together with blood and urine chemistry has lately been shown to be of great diagnostic value [1309] The course is almost always fatal but with modern treatment health may be restored to such a large measure that cure may seem to be accomplished yet sudden death *may occur from trivial* causes [1310] The cause of the syndrome is destruction of the adrenal cortex due in 9 out of 10 cases to tuberculosis

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[1306] Goldzieher M A The Adrenal Gland in Health and Disease Philadelphia 1944 F A Davis Company

[1307] Addison T A Collection of the Published Writings of the Late *Thomas Addison on the* Constitutional and Local Effects of Disease of the Suprarenal Capsules New Sydenham Society 1868 Reprinted in Rowntree and Snell Addison s Disease Philadelphia 1931 W B Saunders Company

[1308] Robinson F J Power M H and Kepler F J Addison Disease—Diagnosis Proc Staff Meet Mayo Clin 16 577-583 1941

[1309] Cutler M H Power M H and Wilder R M Concentration of Chloride Sodium and Potassium in Urine and Blood Their Diagnostic Significance in Addison s Disease J A M A 111 117 12 1938

[1310] *Rowntree L C Report of 3 Cases of Clinical Addison s Disease* Surviving More Than 1 Years Endocrinology 26 793-800 1940



Fig 178 —Addison's disease Patient (left) with her sister for comparison Discoloration only complaint so far Patient died five months later

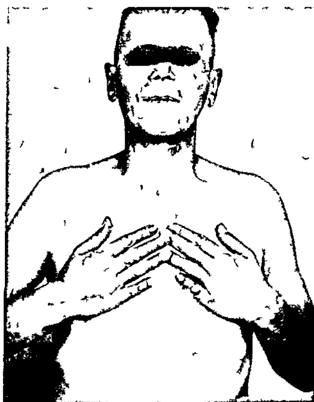


Fig 179 —Addison's disease Note pigmentation of exposed parts (Courtesy Wisconsin General Hospital)

Dermadromes—*Hyperpigmentation* of the skin in connection with destructive adrenal disease is in the vast majority of cases an early symptom often appearing before asthenia and fatigability. Pigmentation about the knuckles may be the first manifestation.[1311,1312]

The fully developed discoloration is uneven in distribution and color. The face, neck, hands and other light exposed parts, the normally pigmented areas, the nipples, the linea alba of women who have been pregnant, the genital region, the gluteal fold and the umbilicus are usually affected first. All areas subject to



Fig. 180.—Addison's disease. Note pigmentation in belt area and over prominent bones. (Courtesy Wisconsin General Hospital.)

pressure, friction and irritation are apt to take on a darker color than the rest of the skin. Thus girdles, garters, shoulder straps, collars, collar buttons and bandages may leave indelible marks. The author saw a deaf woman who was wearing a hearing aid apparatus, the cord of which ran along her back. The slight pressure and friction of this cord had left a deep pigmented mark in the skin at a time when there was hardly any asthenia and little other pigmentation. The creases of the palms and the wrists are sharp dark lines while the palms themselves are still light. Tight skin over bones is often hyperpigmented. Scars, e.g., vaccination marks, have a pronounced tendency to darken early in Addison's

[1311] Rowntree, L. G. and Snell, A. M.: A Clinical Study of Addison's Disease, Philadelphia, 1931, W. B. Saunders Company, p. 176.

[1312] Snell, A. M. and Rowntree, L. G.: Addison's Disease With Anomalous Pigmentation, Endocrinology 13: 303, 1929.

Fig 181





Fig 182

Fig 181 —Addison s disease Pigmentation of palmar creases

Fig 182 —Addison s disease Pigmentation of scars (flat iron burns)

disease Spillmann[1313] advises to watch for the development of pigmentation after the application of an irritant plaster of mustard seed Besides the uneven ness caused by the various terrains great differences in the intensity of the pig mentation occur In some cases the discoloration is blotchy in others irregular and ill defined Some cases present patterns which look like a geographical map especially if much depigmentation accompanies the pigment increase Thus pictures resembling vitiligo may ensue True vitiligo has often been seen to gether with Addison s disease[131] and it is interesting that hypotension has been found in a number of vitiligo cases



Fig 183—Addison di ase De p hyp rpigm ntation and depigmentation urroundi g the anus Whit patient

Leukoderma acquisitum centrifugum (Sutton s disease) and vitiligo have been seen in one case of Addison s syndrome[1314] Some areas of the skin offer a marked resistance to the pigmentation The narrow strip surrounding the lips often stays pale even in extremely dark pigmented cases The same is sometimes true of the fingertips and nailbeds and the backs of the hands to a certain extent also of the eyelids The circumoral strip often remains relatively white in other pigmentations as well for example in the form of discoloration which has been described by Poor[557] as chloasma periorale virginum

The color of the Addison melanoderma is most commonly a tan[1311] but may vary from slate amber or brown shades to the dark black of a full blooded Negro This latter however is very rare The depigmentation of the circum

Spillman L D rm toses en rappo t avec d s troubles des glandes endoc ines et de la nutrition Nouvell Pratique Dermatologique Vol 5 Pa is 1936 Masson & Cie pp 665- 34

[1314] Obermay r M F Leukod ma Acquisitum centrifugum and Vitiligo in a Pati nt With Addi son s Disease Arch. D rmat & Syph 35 370 193

PLATE III

1 Addison s disease Advanced ca e

2 Addison s disease Pigmented palmar crease

3 Addison s disea e Pigmentation of the tongue

4 Addison s disease Pigmentation of the gum

5 Hemangioma of pregnancy Recurring in several pregnancies and receding spontaneously after childbirth (Patient of Dr J Barrock)

6 Kraurosis vulvae multiple carcinomas





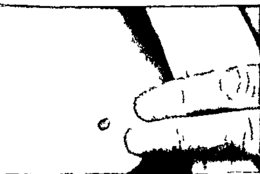



Plate III

Fig 184



Fig 185



Fig 186



Fig 184 — Addison's disease Pigmentation of labial mucosa
Fig 185 — Racial pigmentation of oral mucosa
Fig 186 — Addison's disease Pigmented spot in gum

oral area and of the nailbeds is most striking in such cases. Jet black freckles are often seen, mainly in areas exposed to light but even in unusual places like the palms and soles.[1311]

The lips and the oral mucosa almost always show quite sharply outlined slate or bluish spots, sometimes streaks. They resemble those seen in the mouth of the Negro. They appear rather early in the labial, buccal or palatal mucosa, sometimes on the tongue. The conjunctivae and the sclerae of the eyes, as well as the vagina, may participate in the general hyperpigmentation. Melanosis of the rectal mucosa has not yet been demonstrated. A number of cases of Addison's disease in the Negro have been recorded. Here the Addisonian pigment may be superimposed on the natural pigment so that the palms and soles become darker and an extremely dark color of the rest of the skin results.

Montgomery and O'Leary[1315] emphasizes the relative softness of the skin which he relates to the flattening of the rete ridges and the thin but not atrophic epidermis. Sweating is often pronounced. Some believe the sweat to have a fishlike odor.[1298] In prolonged cases the hair may become darker, particular coarseness or hypertrichosis is denied.[1315] Premature graying and scantiness of the hair has been observed in the course of the disease.[1316, 1317] The frequent shedding of the axillary and pubic hair is emphasized by Albright.[1318] The nails may rarely take on a yellowish hue. Usually they stay pale.[5-9]

Histopathology and Pathogenesis.—The pigment is melanin and as such it is free of iron. It is accumulated in the tops of the basal cells of the epidermis. Dendritic chromatophores are also found in the cutis.[1315] Bittorf[1319] tried to explain the pigmentation in Addison's disease by assuming a higher oxidase content in the skin. His experiments with the skin of patients with Addison's disease were not confirmed by B. Bloch[1320] and his school who believed that not the increased oxidase content of the skin but an increased amount of melanogens accounts for higher melanin production. It was suggested that in the disturbed adrenals less tyrosin might be changed into adrenalin and thus more tyrosin might be available as a promelanin. Later (1928) Szent Györgyi[1321] who isolated vitamin C from normal adrenals advanced the theory that the high reducing power of this substance (then called hexuronic acid) serves as a control in the oxidation of promelanin to melanin in the normal skin. Its deficiency caused by destruction of the cortex would increase the oxidizing power of the skin and thus enhance the melanin formation which is an oxidation process. A great deal of experimental work seems to corroborate the antipigmentogenic role of vitamin C.

1315 Montgomery, H., and O'Leary, P. A.: Pigmentation of the Skin in Addison's Disease, Acanthosis Nigricans and Hemochromatosis, Arch. Dermat. & Syph. 21: 970-984, 1930.

1316 Bauer, Julius: Inn. Sekretion, Berlin, 1927, Julius Springer.

1317 MacBryde, C. M.: Addison's Disease, M. Clin. North America 26: 391-400, 194[illegible].

1318 Albright, F., Smith, P. H., and Fraser, R.: Syndrome Characterized by Primary Ovarian Insufficiency and Decreased Stature, Tr. A. Am. Physicians 57: 219-226, 194[illegible].

1319 Bittorf: Pathologie der Nebennierenerkrankungen, Jena, 1908. Ueber die Pigmentbildung bei der Addisonschen Krankheit, München. med. Wchnschr. 70: 30-23, 1923.

1320 Bloch, B., and Löffler, W.: Untersuchungen über die Bronzefärbung der Haut bei der Addisonschen Krankheit, Deutsches Arch. f. klin. Med. 211: 262, 91, 1917.

1321 Szent Györgyi, A.: Observations on Function of Peroxidase Systems and Chemistry of Adrenal Cortex: Description of New Carbohydrate Derivative, Biochem. J. 22: 1387-1409, 1928; also On the Chemistry of the Adrenal Cortex, Am. J. Physiol. 90: 536, 1929.

It is well known that lemon juice which has a high vitamin C content prevents the blackening of cut surfaces of fruit e g avocado pears and inhibits the oxida tive dopa reaction [13] Vitamin C is also able to bleach pigmentations including those of Addison s disease

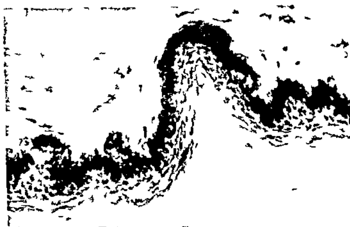


Fig 187 — Addis n s dis as (Courtesy Div ion of D rmatology D partment of Medicine University of Chicago)

Pigmentation of the skin and melanogen formation in the urine after exposure to light can be inhibited by previous administration of vitamin C [1323 13 4] W Jadassohn and Schaaf [13 5] however showed that even large amounts of vitamin C could not prevent the pigmentation produced in guinea pigs by estrogens and other authors[13 6] believed that the concentration of vitamin C in the human serum would not be strong enough to inactivate the dopa oxida e and to inhibit the dopa reaction as it does in vitro In this connection the vitamin C deficiency in pregnancy which is a period of increa ed pigment formation may be mentioned

The theory of the pigmentation inhibiting power of vitamin C would be in line with Bittorf s[1319] opinion that it is the higher oxidizing power and not the higher amount of melanogen which cau es the Addisonian pigmentation

Szent Gyorgyi [1321] in accordance with Bloch and Loffler s[13 0] work tried to link the theories by suggesting that vitamin C deficiency which also leads to decreased production of adrenalin might thus keep more melanogen available for production of melanin Adrenalin is closely related to several of the melan ogens (pyrrol tyrosin dopa etc) If this double pigmentogenic role of vitamin C should be confirmed it might help to explain the high degrees of pigmentation reached in Addison s disease

[23] St pp W Kühn u J and Schroeder H Di Vitamine Stuttgart 1938 Ferdinand Enke

[13] Schad H A Beitrag zur F g d s Einfl sses von Vitamin C (l Ascorbinsäu e) auf Pig menti rungsvorgä g Klin Wchnschr 14 60-61 1935

[1 4] Fahler H and La Croix V Uel d n Ei fl ss der Ascorbinsäure auf die M lanogenaus scheidung Kli Wchnschr 14 1851 1853 193

[13 5] Jadassohn W and Schaaf F D pigm ntier nde Wirkung d r 1 Ascorbinsäure (Vitamin C) Kli Wchnschr 13 845-846 1934

[13 6] Fantl P and Fessl r A Vitamin C a d Dopareaktion Klin Wchnschr 14 576-577 1935

Hyperpigmentation has been observed in true scurvy. This observation could be used as another argument in favor of the vitamin C theory of the Addisonian pigmentation. Difficult to reconcile with the outlined role of vitamin C is the observation that this substance occurs together with melanin in the human skin.[1327] Lately (Edelbacher and Zeller quoted by Robert and Zeller[1328]) the experimental formation of melanin from histamine by the enzyme diamin oxydase (DO) has opened a new path. In adrenalectomized animals the formation of the histamin decomposing enzyme DO is disturbed. But not more than this hint of a relationship has so far been given. A definite explanation of the pigmentation in Addison's disease has not yet been found.

Recently the role of the sympathetic system in the pigment formation in Addison's disease has again been emphasized.[1329] The disturbance of the sympathetic system caused by the destruction of the adrenal cortex may lead to melanosis. Hyperpigmentation due to destruction of the plexus coeliacus and other sympathetic structures by neoplasms, aneurysms or injuries is well known[1329] see also acanthosis nigricans, nervous system.

Treatment.—The treatment of the pigmentation in Addison's disease has hardly been tried by other methods than those directed towards the adrenal insufficiency. Four important advances have been made during the last decade.[1330] These are (1) the introduction of salt therapy, (2) the restriction of potassium salts, (3) the elaboration of potent extracts of the adrenal cortex and (4) the synthesis and availability of desoxycorticosterone esters. It seems, as was to be expected, that their value is due to the fact that they maintain life, not that they cure the destructive process in the adrenal cortex, just as insulin does not cure diabetes. In spite of the sometimes dramatic effect on most of the symptoms[1331] the fully developed pigmentation is hardly ever reversed. This opinion of investigators who treated many cases of Addison's disease is in contrast to other reports.[116, 1311, 1330] Dehydration in times of remission and while under treatment with desoxycorticosterone and salt may make the patient appear lighter in color. The pigmented spots in the mouth will rarely disappear under any form of treatment.[1333] In the rare cases of syphilitic Addison's disease complete disappearance of all symptoms including pigmentation has been seen. But unfortunately the vast majority of the cases of Addison's syndrome are due to tuberculosis.

Some metabolic parallels of adrenal insufficiency and pemphigus, especially the lowering of the chloride and protein level and the increase of the plasma volume and interstitial fluid have led to encouraging trials of desoxycorticosterone acetate

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1327 Co nt leet T Vitamin C a d Pigm t A ch D mat & Syph **35** 471-479 1937

1328 Rob rt I and Zeller F A Pigm nt Formation and Di mine Metabolism R6l of D pa O idase Schweiz med W hnschr **71** 160 1607 1941

1329 Von Kup T Hautmelano e und Nebennieren Vi chows Ar h f p th Anat **309** 711-717 1942

1330 Loeb R F Adrenal I uffi i ncy Bull N w York A a i Med **16** 347-367 1940

1331 Rowntree L G Results of Treatm nt i Addison s Diseas M Clin N rth Am ri a **24** 1779-1787 1940

1332 Sézary A Path géni t s miologie d s méla odermies du type a1 lie i Pr ss méd **29** 281 1921

1333 Loeb R F Adrenal Cortex Insuffici n y J A M A **116** 49- 00 1941

(doca) in pemphigus[1334, 1335] The recommended dose is 5 mg 3 times daily for 3 weeks and 5 mg daily thereafter Autoptic findings of severe adrenal lesions in pemphigus have been reported by Goldziher[1336]

Adrenal Tumors and Hyperplasias

Adrenal cortical tumors and hyperplasia of the adrenal cortex produce a syndrome which has received several names Hirsutism[1337] which refers to the main feature of hypertrichosis is most often used Other terms are hyper adrenalism genitosuprarenal syndrome and genitosuprarenal virilism The term interrenalism[1338, 1339] refers to the interrenal organ of the elasmo branch fishes which instead of adrenals have an elongated body between the kidneys closely resembling in its histology the mammalian adrenal cortex Lately the syndrome of rapidly acquired obesity of the trunk kyphosis and round shoulders striae dusky skin and hirsutism amenorrhea or impotence hypertension and fatigability has often been referred to as Cushing s syndrome[1340] even if it is not associated with Cushing s disease basophil adenoma of the pituitary Primary adrenal tumors of the cortex as well as of the medulla are very rare Gibson[1341] found only one in approximately 12 000 admissions to the University of California Hospital

The adrenal cortical tumors or hyperplasias which produce the syndrome of hirsutism occur in females in 80 per cent of the cases A considerable number has been found in young children even in the newborn[1342] The cortical neoplasms observed so far have been carcinomas benign adenomas sarcomas and metastatic growths from cancer of the breast or of the stomach The localization in the cortex rather than in the medulla is more important in the production of a typical syndrome than the histology of the tumor Very small adenomas may cause fully developed hirsutism No parallelism exists between the size of the neoplasm and the degree of the syndrome The hyper nephromas (Grawitz s tumors) do not cause hirsutism In several instances highly malignant cortical neoplasms were found without having produced the syndrome of hirsutism[1343] (Wu quoted by Kepler and Keating[1306])

Dermadromes —The syndrome caused by adrenal cortical tumors is modified by sex and age In small boys precocious puberty with enlargement of the

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1334 Talbott J H and Co mb F S P mphigu Arch D mat & Syph 41 3 9-369 1940

1335 Col lma A Ma kham M J a 1 S haff r A J Cas of P mphigus Treated With Desoxy co ticost rone A tate J Clin Endocri ol 2 343 344 1942

1336 Gol lzih J W Ad al Glan is i Pemphigus Vulgari Ar h De mat & Syph 53 4 -44 1946

1337 Ap t F ur l hirsutLm Bull t mém Soc méd d Hôp de Paris 41 131 1925

1338 Mathias F l l r A d utu gsfo m n on I te renalismus Zentralbl f Gynäk 50 480 49 19 6

1339 Wright S Applied Physiology N w Y k 1940 Oxford Univ rsity Press

1340 Warren F L Estimation of Urin ry ketosteroids in th Di gnosis of Adrenal Cortical Tumors Ca cer Research 5 49 51 1945

1341 Gibson T F Th Diag osis of A lrenal Tumors With Classification of Ad enal Tumor Syn dromes Cases J Urol 18 33 9 19 7

1342 Bay r G and Lang F J t be M crosomia Int rrenali Cong nita E dok i ologi 14 2 5 1934

1343 K pl r E J nd K ating F R Jr Diseases of th Ad al Glan I II Tumors of the Ad nal Cort x Di ases of th Adre l Medulla an I Allied Di turbances Ar h Int Med 68 1010-1036 1941

penis hypertrichosis and muscular development create the type known as the infant Hercules Even paternity has been reported[1344] In adult males[1344] gynecomastia feminine habitus disappearance of the beard and a decrease in the size of the penis and testes have been observed Less than ten cases of this particular condition have been reported[1345 1346] In small girls precocious puberty hypertrichosis obesity and virilism are the rule while in adult females amenorrhea and virilism dominate the syndrome Sometimes even baldness of the male type and a mustache will develop The breasts decrease in size This group is the largest But it must be kept in mind that these syndromes are not pathognomonic for adrenal cortical lesions alone Similar changes have been seen in basophilic pituitary tumors various intracranial diseases hyperfunctioning gonadal tumors thymus tumor[130] and other rare conditions (see chapter on puberty)

Hypertrichosis is the outstanding dermadrome in cortical tumors It is an almost obligatory early conspicuous and sometimes even monstrous manifestation However it is by no means diagnostic of adrenal cortical tumor Not only does it occur in the above mentioned conditions but marked degrees of *hypertrichosis are frequently seen in apparently healthy women with no symptoms* of any endocrine disorder (See also chapter on Pregnancy) Hirsutism in children with adrenal cortical tumor has been observed as early as the first year of life even in the newborn There are reports of young children with beards pubic and axillary hair and heavy and pigmented lanugo growth of girls of nine with bushy eyebrows and of boys of the same age who had to have daily The pubic hair growth in these cases usually resembles the male type *The pubic change may be unilateral*[134] *High urinary androgen output has been* observed[1348]

In adult women hirsutism can produce the most unusual pictures You should be women and yet your beards forbid me to interpret that you are so (Macbeth I 3) This best characterizes the impression one gets of some fully developed cases Some of the bearded women of the circus side shows belong to the adrenal group The pubic hair changes to the male type The lanugo becomes pigmented and in some parts of the body over an inch in length Long pigmented hairs in the areolae of the nipples and coarse hair in the skin over the sternum and frequently on the mammae are conspicuous Unusually long eye lashes have been seen[1349] In contrast to the general hirsutism *is the loss of head hair in women with adrenal cortical tumor resembling the male* baldness[1344 1350]

[1344] Looney J M Sex Factors of the Adrenal Gland Endocrinology 27 511 0 1940

[1345] Kepler E F The Adrenal Gland Paper read before the Medical Society of Milwaukee County Nov 21 1939

[1346] Holl Gundaker 2 männliche Fälle von Nebennierenrindentumoren mit innersekretorisch Störungen Deutsche Ztschr f Chir 228 277 29 1930

[1347] Bissell G W and Williams R H Hirsutism in Females Am Fed Clin Research (1943) 1 38-39 1944

[1348] Dorfman R J Wilson H M a Peters J I *Differential Diagnosis f Basophilism (Cushing) and Allied Condition (Cortical Tumors and Arrhenoblastomas)* Endocrinology 27 1 15 1940

[1349] Reitter C Ein Fall mit abnormem langen Cilien Ztsch f Augenh 73 357 1931

[1350] Bauer J Lebensfunktion des gesamten Nebennierensystems ohne anatomischen Befund Wien klin Wchnschr 43 55? 5?6 1930

Changes of the *pigmentation* in adrenal cortical tumors include occasional increased pigmentation around the nipple in adult males and in females pigmentation of the linea alba and the vulva comparable to that of pregnancy

Unusual *acne* and comedos either in small children or in adults is almost invariably seen in cortical tumors [1351] The acne itself often seems to differ from the typical juvenile form and resemble the severe pyodermatic type known as acne conglobata [1343]



Fig 188 — Adrenal cortical carcinoma Hyperpigmentation (Courtesy Wisconsin General Hospital)

The amazing symptoms of *precocious puberty* in adrenal cortical tumors have led to the publication of a great number of almost identical cases Besides the hair changes which have already been mentioned menstruation in early childhood and breast development have often been observed Growth of the clitoris to an erectile penis with glans corona and a hypospadic groove on the ventral surface with the labia minora shaped like a prepuce and the labia majora like a scrotum adds to the monstrosity of the syndrome Such girls may have a deep voice The whole body of these patients may show unusual growth with or without obesity and hirsutism The infant Hercules a sturdy little man with unusual muscular and intellectual development and with a large erectile penis is the rare counterpart in boys The skin of the entire body is often mottled with dusky purplish red areas similar to cutis marmorata [1343] The features in precocious puberty are bloated the complexion dusky and congested

Obesity is not uncommon in cases of adrenal cortical tumor but it is more the distribution of the fat which is striking than the actual amount The com

[1] Wintersteiner O The Adrenogenital Syndrome J A M A 116 26 9-2653 1941

bination of the full face the pad in the high dorsal region and the heavy abdomen together with the thin extremities creates a characteristic habitus [1343]

Next to the pituitary basophil adenoma cortical tumor of the adrenal is the condition which is most frequently connected with *Cushing s syndrome* [1301]

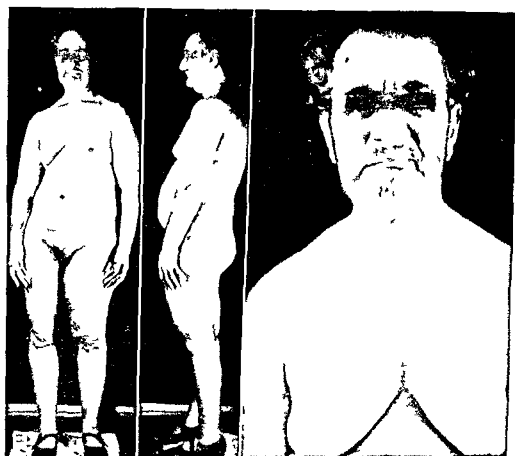


Fig 189—Achard Thiers syndrome (diabetes in bearded women) (From Pullen R L and Sodman W A J Clin Endocrinol Courtesy of Charles C Thomas Publisher Springfield Ill)

Some of the cases of so called *diabetes of the bearded women*[135] belong here In about 25 per cent of the reported cases hypertension amenorrhea obesity and acneiform eruptions have been noticed [1344 1353]

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[13] Achard C h a d Thi rs J Le virilism pilair et son a sociation à l in ufflsance gly olytiqu (diabète des femmes à barbe) Bull Acad de méd Paris 86 51-66 1921

[1353] Sh par ison H C a d Shapiro F Diabetes of Bearded Women Endocrinology 21 3 5? 1939

The urinary output of androgens (17 ketosteroids) is often high in adrenal cortical tumors[1344, 1354–1356] There is a general tendency to interpret Cushing s syndrome with or without pituitary adenoma as caused by hyperadreno cor ticalism[1357, 1358] Striae have been seen to appear after the injection of adrenal cortical extract The diagnosis of adrenal cortical tumor is mostly suggested by the described symptoms But however striking they are all or some may be absent and in spite of their presence no adrenocortical tumor may be found The similarity of symptoms in other conditions has been mentioned The roent genographic demonstration of cortical lesions by air injection into the perirenal fascial spaces is possible but difficult and not without danger In recent years estrogenic and androgenic substances substances which prolong survival of adrenalectomized animals and inactive substances which are chemically related to hormones have been found in the urine of patients with hyperfunctioning cortical lesions[1306, 1343] But these findings are no more constant than other signs and symptoms Many of the organic changes even the monstrous symptoms of feminization and masculinization are reversible if the cortical tumor is removed However since most of these neoplasms are malignant only few patients live long enough to experience the return of normalcy No confirmed dermadromes have become known in tumors of the adrenal medulla

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[1354] Crook A C and Gallow R K The Differential Diagnosis of Basophilism (Cushing s Syndrome) by the Estimation of Urinary Androgens Quart J Med 8 33 249 1939

[1355] Anderson A F Hain A M and Patterson J Adrenal Carcinoma Hormonal Diagnosis From Excretion of Pregnadiol J Path & Bact 55 341 349 1943

[1356] Hirschmann H and Hirschmann F B Steroid Excretion in Case of Adrenocortical Carcinoma J Biol Chem 157 601 61 1945

[1357] Albright F Cushing Syndrome Harvey Lect 38 125 180 1943

[1358] Anderson E and Haymaker W Cushing Syndrome J Nerv & Ment Dis 99 511 5 0 1944

Hohneck I Über das Auftreten und Entstehen der Striae cutaneae distensae Med Welt 10 1071 10 2 1936

CHAPTER XIX

DISORDERS OF THE ENDOCRINE GLANDS

THE TESTICLES

The gonadotropic hormone of the anterior pituitary stimulates the Leydig cells in the connective tissue stroma of the testicle to produce the male sex hormone testosterone. It is excreted in the urine as androsterone which is a 17 ketosteroid. Both forms are often referred to as androgens. The international unit is the capon unit which is the biological equivalent of 100 micrograms of androsterone. Wolf[1] [98] *enumerates as functions of testosterone the development* and maintenance of the accessory sexual apparatus, the growth and distribution of hair, the maturation of the skeleton, the larynx and the muscles, the distribution of fat, the control of libido and potency and the determination of the masculine psychological pattern. The excretion of androgen which is only 1 to 15 I. U. per day in childhood rises at puberty to 40 to 60 I. U. in the male and 25 to 40 I. U. in the female. The reverse relationship prevails with regard to estrogenic hormone output. Beyond the age of 60 the androgens decrease[1360] but do not completely disappear as is the case with estrogens in old women.[1295]

The androgens are chemically only slightly different from the estrogens, cholesterol and the bile acids (see also introduction to chapter on puberty).

Many facts demonstrating the influence of the testicle on the skin of animals are known.[1361] The best studied is the growth of the comb of the cock. Well known are the modifications of the plumage in male, female and castrated chickens. In some species, however, e. g. the guinea fowl, the plumage is not dependent on the gonads. The castrated male deer develops a peruke, a hairy growth instead of the antlers. In the reindeer which has antlers in both sexes castration is not followed by this malformation. In the Egyptian antelope *Portas pictus* the male is gray and the female brown. The hair of the castrated male takes on the same color as the female (Zawadrosky after Sand[1361]).

Comparable to the gonadal relations of the apocrine glands in man are the atrophy of the preputial glands in castrated mice[136] [1363] and of the scent glands in the male goat.[1364] The improvement of the pelt in spayed animals[1365] [1366]

[1360] Buhler F. Sexualhormonb fund in Harn von Männern verschiedenen Alters. Ztschr. f. exper. M. 1 86 6 0-658 1933.

[1361] Sand, I. Die Physiologie des Hodens. Handb. d. inneren Sekretion vol. Leipzig 1933 Curt Kabitzsch.

[1362] Voss H F. Die Präputialdrüsen der Maus in ihrer Abhängigkeit vom Hormon des Hodens. Ztschr. f. Zellforsch. u. mikr. Anat. 14 00- 1 1931.

[1363] Buschke W. Die Hautdrüsenorgane (Harder'sch. Drüsen, Inguinaldrü. Präputialdrüsen, Analdrüsen, Kaudaldrüsen, Ii f rdrü n d r Laboratoriumsnagetiere und die Frage ihrer Abhängigkeit vom Geschlechtsleben. Ztschr. f. Zellforsch. u. mikr. Anat. 18 217 43 1933.

[1364] Chatagnon, A. Action de la castration sur les glandes odorantes du bouc. Compt. rend. Soc. de biol. 108 631 1931.

[1365] Schmidt, F. Fellverbesserung durch Kastration. Kl. intl. f. u. Pelzti. r p 233 1931.

[1366] Jolly, zo a. Der Einfluss der Hypermaskulinisation nach Voronoff auf die Produktion der Wolle und d. Entwicklung der Körperform des Schafes. Trudi gosud. Inst. ek. per. v. t. 9 52 79 1930.

seems to be in contradiction with the favorable effect on the fur following the administration of testosterone or transplantation of testicular tissue in senile dogs[1367] Castration and testosterone treatment demonstrated the gonadal dependence of the striking fur characteristics of the male baboon[1368] The pigment formation in man is also stimulated by testosterone (Milro after O Henslein 41)

The reduction of the readiness for anaphylaxis by removal of the testis and the restoration of a normal capacity for allergization by hormonal substitution has been demonstrated by Yun (after E Urbach) The number of mitoses in the epidermis and hair follicles of the male white mouse decreases substantially after castration[1369]

Much evidence has been accumulated suggesting a stimulating effect of androgens on number size and function of the sebaceous glands oil glands and thickness of the epidermis[1370,1371] and an increase of the production of prepucial smegma[137] Acne hirsutism obesity husky voice and enlargement of the clitoris has been observed in women who have been treated with testosterone propionate because of menstrual disturbances[1373] Folliculitis of the nose and of other parts of the skin and acne occur sometimes in men who receive androgenic therapy

Eunuchism and Eunuchoidism

Eunuchism is the syndrome resulting from loss of the testes while eunuchoidism characterizes the state of gonadal deficiency in the male *

Early Castration—Loss of the testicles before puberty causes prolonged patency of the epiphyseal clefts with resulting excessive length of the extremities and fingers The voice does not change the muscles fail to gain the masculine strength and no libido develops

Dermadromes—Most striking is the failure to develop the sexual characteristics The penis remains small and may be retracted into the scrotal skin which is thick and not unlike the labia majora The body hair is scanty and the beard is absent with the exception of a little lanugo on the upper lip In later age a scanty and bristly old women s beard appears on the chin and around the angles of the mouth If there is a development of pubic hair it is of the female type The hair line along the forehead does not develop the temporofrontal

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* The terms eunuchism and eunuchoidism should be reserved for gonadal deficiencies in the *male*

1367 Zahl H R Juvenation of Senile Dogs by Means of Testicular Preparations and Their Effect on Testicles and Prostates Virchows Arch f path Anat 305 65-107 1939

1368 Zuckerman S and Parkes A S Secondary Sexual Characters in Monkeys (Castration) J Endocrin 1 430-40 1939

1369 Ortiz Picón J M On the Effect of Castration on the Proliferative Activity of the Epidermis and of the Hair Follicles R Españ biol 2 43-46 1933 Zbl 48 11

1370 Hooker C W and Pfeiffer C A Growth Effects of Sex Hormones Upon Body Growth Skin Hair and Sebaceous Glands in Rats Endocrinology 32 69 76 1943

1371 Rony H R and Zakon S J Effect of Androgen on the Sebaceous Glands of Human Skin Arch Dermat & Syph 48 601-604 1943

1372 Hamilton J B Male Hormone Substance Prime Factor J Clin Endocrinol 1 570-592 1941

1373 Greenhill T D and Freed J C Virilism in Women Caused by Androgenic Therapy for Menstrual Disturbances J A M A 112 1573-1574 1939

notch which is to a large extent characteristic of the male It stays straight or is gently rounded (see puberty) The scalp hair seems to be vigorous The same is sometimes true of the eyebrows and eyelashes (H Fischer after Lowenthal [1374, 1375]) Some authors however emphasize that the eunuchs fail to develop bushy eyebrows which are seen in many men after the fourth decade [1376] It is known since antiquity (Artistotle) that eunuchs do not become bald headed like many other men However precocious graying is mentioned [1377]

Late Castration —If the loss of the testicles occurs after puberty the changes are less pronounced and even libido and potency may remain to some degree The observations on such cases are plentiful Hot flashes are felt by some castrates shortly after the loss of the testicles but they do not become as distressing a symptom as sometimes occurs in the female climacteric There is a tendency towards loss of body hair[1378] which usually takes on a female distribution [1379] A patient of Lisser[1384] who shaved four times weekly before the loss of his testicles had to shave only once a week afterwards In some adult castrates the beard remained unaffected [1298, 1379]

The skin of the eunuchs is rather thin and remarkably pale with a slightly yellow hue The *pallor* which is an outstanding characteristic of the eunuch s skin is caused by narrowing of the arterial bed and by a relative lack of melanin resulting from the failure of a colorless promelanin to mature to dark melanin Probably because of this fact there is little or no tanning on exposure to ultraviolet light [1380] Similar phenomena are known in the female (see menstruation) Castrates who work outdoors like some members of the Skoptsy a religious *sect in Russia and Rumania which practices castration for religious reasons* do not acquire the typical farmer s skin [1376, 1381, 1382]

The yellow component of the castrate s skin is caused by carotene which is present in excessive quantity [1380] Pallor pigmentation and carotene content can be influenced by testosterone administration The panniculus adiposus is often increased with concentration on the thighs the hips and the abdomen Weight gains of twenty five pounds are common and the basal metabolism is usually lowered [1379] Some eunuchs however are lean Gynecomastia is common[1383] but the breasts consist of fat only and not of glandular tissue [1374]

[1374] Löwenthal K Der Eunucholdismus des Mannes Beitr z path Anat u z allg Path 86 426-439 1931

[1375] Scheuer O F Die Behaarung d Mensch n Leipzig 1933 Curt Labitz ch

[1376] Tandl r S and Gross J Die Skopzen Einfluss der Kastration auf den Organi mus Arch f Entwcklingsmechn d Organ 30 2 235-253 1910

[1377] Marañon G Manual de las enfermedades endocri as y del m taboli mo Libreria Hach tt Buenos Aires 1933

[1378] Hackfield A W Ueber die Kastration bei 40 s uell Abnorm n Monatschr f *Psychiat* u Neurol 87 1-31 1933

[1379] McCullagh E P and Renshaw J F Effects of Castration in Adult Male J A M A 103 1140-1143 1934

[1380] Edwards E A Hamilton J B Duntley S A and Hubert G Cutaneous Vascular and *Pigmentary Changes in Castrate Men* Endocrinology 28 119 1 8 1941

[1381] Koch W Die russisch armenische Kastratensekte der Skopzen Veröffentl a d K iegs u Konstitutionspath 2 1-33 1921

[1382] Pittard E La castration chez l homme Rech rches sur les adeptes d un ecte d eu uques mystiques les Skoptzy Arch suis e d anthrop gén 6 213 236 1933

[1383] Lange J Die Folg n der Entmannung (an Hand der Kriegserfahrungen dargest llt) Leipzig Georg Thieme 1934

The face often has a sleepy expression This is caused by a small fat pad in the upper eyelids which narrows the space between the lids Slight puffiness of the face is an early and common symptom after adult castration [1383] The face often becomes finely wrinkled in a peculiar shriveled or papyraceous way which does not correspond to the normal facial folds

Increase of the thickness of the nails in an adult castrate which could be reversed by testicular substance was seen by Lisser[1384] although nail changes were missed in the twelve cases of McCullagh and Renshaw [1379]



Fig 190 — Eunuchoid in a young man aged 18 years Beard axillary chest pubic hair absent Fronto-temporal hair line without masculine notch

All or some of the features of eunuchism may be seen in the syndrome of eunuchoidism which is not rare as the experiences in the military induction centers have shown Heredity is a factor in this constitutional endocrine anomaly [1374 1385]

The *male climacteric* is an objective reality [1386] and not mainly a matter of neurasthenia and hypochondry [1387] However no definite dermadromes which

[1384]Lisser H Onychauxis in an Eunuchoid Remarkable Improvement by Implantations of Testicular Substance Arch Dermat & Syph 10 180-187 1924

[1385]Carmichael H T and Kenyon A T Eunuchoidism Arch Neurol & Psychiat 40 717 742 1939

[1386]Heller C G and Myers G B The Male Climacteric J A M A 126 472 1944

[1387]Blum V Das Problem des männlichen Klimakteriums Wien klin Wchnschr 49 1133 1139 1936

are linked to the physiological decline of the testicular function have become known The keratoderma palmarum et plantarum climactericum described by Haxthausen in the female has also been reported in ageing men[1388] In a recent analysis of 54 cases of the male climacteric[1389] itching hot flashes and sweating occurred in about one third of the instances Androgenic therapy seems to be promising

Common Baldness

Since the common type of baldness occurs almost exclusively in men it is natural to think of causes peculiar to the male sex R O Stein[1390] who first described the calvities frontalis (see puberty) which is largely characteristic of the male hairline and is usually lacking in eunuchoids and women has suggested that the common baldness of males is a continuation of the physiological frontal baldness Seborrhea and tension of the scalp with impaired circulation are contributing factors Several authors[1391, 1392] suggest that baldness of the common type is a generalized primate trait which occurs in a similar pattern in apes and monkeys Heredity is a definite factor[1393, 1394] In 1932 Sabouraud[1395] quoting the famous observation of Aristotle that neither the child nor the woman nor the castrate become bald added that we know hardly more on the subject The situation does not seem to have changed However we have learned that administration of male hormone to eunuchoids and castrates can produce baldness of the common type Premature alopecia of the male type has also been seen in virile women with arrhenoblastoma or suprarenal virilism It ceases to progress when the abnormal masculinization ends[1394]

Unfortunately endocrinology has not yet shown a practical way to prevent or cure baldness Castration prevents baldness but this surgical approach has so far not been suggested in seriousness though it has been hinted

Gynecomastia

Gynecomastia may occur in an otherwise normal puberty Ten cases were recorded per 100 000 personnel in the United States Navy[1395] The type occurring in otherwise normal young men is more often unilateral than bilateral[1396] It is also occasionally seen in the male climacteric[1397] It is often pronounced in Fröhlich s syndrome and in eunuchoidism In rare instances it is associated with a variety of neoplasms which have retained the endocrine functions of the

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1388 Henschen G Palmar and Plantar Keratoderma Schweiz med Wchnschr 70 690-691 1940

1389 Werner A A Mal Climacteric 54 Cases J A M A 127 70 710 1945

1390 Stein R O Über die Beziehung des Haarwachstums und Haarausfalles zum endokrinen System und über die Möglichkeit einer endokrinen Therapie der Glatze Wien klin Wchnschr 49 449-452 1936

1391 Miller G S Jr Human Hair and Primate Patterning Smithsonian Misc Collect 85 10 1931

1392 Rattner H Ordinary Baldness Arch Dermat & Syph 44 201 213 1941

1393 Osborn D Inheritance of Baldness J Hered 7 347 1916

1394 Hamilton J B Mal Hormone Stimulation is Prerequisite and Incitent in Common Baldness J Invest Dermat 6 473-4 4 1942

1395 Weber G A Gynecomastia in the Navy Mil Surgeon 85 375 379 1941

1396 Menville J G Gynecomastia Hyg la 11 157 158 1933

1397 Richardson T S Gynecomastia Lancet 1943 1 304 30

soil from which they originated Such tumors include[1398,1399] instances of adrenal cortical tumor[1344,1400] eosinophil adenoma of the anterior pituitary pinealeoma neoplasms of the midbrain or of the hypothalamus and thymic tumors The best known endocrine neoplasmatic cause however are tumors of the testicle especially teratomas and the rare chorionepitheliomas with high estrogen production[1401,1406]

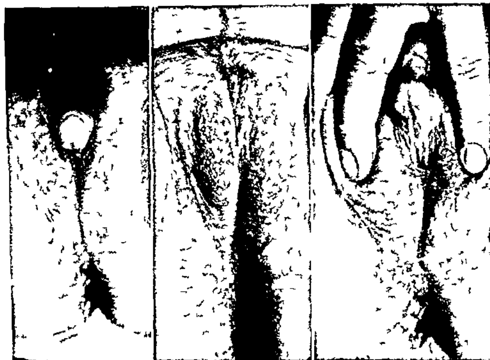


Fig 191 I g 19 Fig 193

Figs 191 192 193 —Pseudoh maphroditi m Fe nale aged 19 y ars Ovaries infa itile ut rus agina f 10 m length f male dist ibution of pubic hai but erigi l phallu of 4 cm scrotal app ar a ce of lat la major m l b ea ts male body co figuratio husky voic vigorous beard growth Live as a girl (Court y Wisconsin Gen ral Ho pital)

[1398] Webe F I Gynecomastia—En loc ine Tum rs M Press 211 155-157 1914

[1399] K iss B U ber Gynäkomasti in B itrag ur Kenntnis d r Bezi hungen zwisch n Keim drü n un l Geschlechtscha a t ren Arch Gynäk 141 503 539 1930

[1400] Geschickt C F Sup aren l Tumors Am J Cance 23 104 124 1935

[1401] Stori h nn K R Ein Fall v n Chorionepitheliom im Hod n mit Gynäkoma tie Fra kfu t Ztsch f Path 43 80-95 1932

[1402] J rdans G H W Gynäkomasti bei inem krank n mit malign m Testi t ratom Ned rl tijdschr v g neesk 77 2915-20 3 1933 Zbl 46 189

[1403] Zond k B Malign Hod ntumoren und Hypophy n ord rl ppenh rmon Ho mo al Diagnostik au H rn Hydrocel nflüssigk it un l Tumorgew be Klin Wchnschr 11 74 270 1932

[1404] Gordon W G Pathology of 142 Cases of Primary Neoplasm in Man J Urol 43 72 733 1940

[1405] Lewin M L Gynecomastia J Clin Endocrinol 1 511-514 1941

[1406] Bonn H K and Evans N Chorio pithelioma in Mal and Gy ecomastia Am J Surg 58 125 132 1942

This symptom has furthermore been seen to follow prostatectomy and the administration of cholesterol[1407] adrenal cortical extract[1408] and desoxycorticosterone (Doca)[1409] It is a frequent finding in cirrhosis of the liver (see chapter on diseases of the liver) Failure of the cirrhotic liver to destroy estrogens may be the cause of gynecomastia in severe hepatic disease[1410] (Zondek B after Edmundson)

Testosterone has been shown to cause complete regression or reduction of the hypertrophy of the male breast in 26 out of 28 cases[1411] Surgery has been recommended[1395]

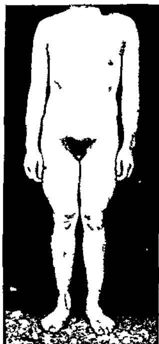


Fig 194 —Same patient as shown in Figs 191 193 (Courtesy Wisconsin General Hospital)

Hermaphroditism

The presence of testicles does not necessarily produce male sexual characteristics Female hair and other sex characteristics have been found together with microscopically verified testicles[1412] In a case of hermaphroditismus veru

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[1407] Dunn C W Stilbestrol—(Estrogen)—Induced Gynecomastia in Male J A M A 115 2 63 2264 1940

[1408] Bronstein T P Gynecomastia Endocrinology 24 274 277 1939

[1409] Lawrence R D Gynaecomastia Produced by Desoxycorticosterone Acetate (Adrenal Preparation) Brit M J 1 12 1943

[1410] Glass S J Edmondson H T and Soll S N Hormone Changes Associated With Liver Disease (Gynecomastia in Cirrhosis) Endocrinology 27 49 75 1940

[1411] Hoffman W J Gynecomastia Hormone Therapy Am J Cancer 36 247 251 1939

[1412] Weisman A T and Schwartz A Intersexuality J A M A 117 2 18-2251 1941

lateralis[1 98] with a testicle in the right side of the scrotum and an ovary and uterus in the left side of the scrotum, breasts pubic hair and other characteristics were of female character [1413] They changed to the male after the removal of the ovary and uterus

Tumors of the Testicles

Except for the symptoms of precocious puberty and gynecomastia which may be caused by tumors of the interstitial tissue of the testicles no skin manifestations seem to be known in tumors of the testicles

[14 3]Lattimer T K Engl E T and Yeaw R C True Hermaphroditism J U ol 50 481-496 1943

CHAPTER XX

DISORDERS OF THE ENDOCRINE GLANDS

THE OVARIES

Our knowledge of the influence of the ovaries on the skin in animals is much greater than that of the comparable facts in man In the capon it is possible to produce a female plumage by injections of folliculines[1414] The feathers of an adult capon are so sensitive to injections of estrogens and placenta extracts that the failure to inject the hormones one day a week in a series of daily injections *is recorded by a black bar in the breast feathers in their regeneration after being* plucked[1415] This pigmentary reaction can be used as a pregnancy test[1416] utilizing urine which can be read in 48 hours In the oophorectomized Leghorn chicken the injection of small doses of theelin in olive oil causes a change in the regenerating feathers from male type back to female so that alternating bands of female and male color can be obtained[1417] While the time for the regrowth of the hair after shaving is the same in both sexes in immature rabbits it is shorter in the mature female longer in the mature female castrate and shorter again in males feminized by estronization[1418] Infiltration of the capon skin with estrogen locally inhibits the characteristic feather changes seen in castrates[1419 14 1] Continued subcutaneous injections of estradiol benzoate produces shagginess and marked loss of hair in the rat The estrogen treated rat has a thinner dermis and epidermis and the sebaceous glands are reduced in size and number All these changes can be prevented by administration of androgen[1370]

The implantation of ovaries into the kidneys of castrated male guinea pigs produces inten e pigmentation of the nipples unless these are situated in albinotic skin[14]

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[1] Carl Irolt F De l action du b oat de folliculi sur le plumage lu co q domesti que Compt rend So de Biol **118** 523 6 193

[5] Juhn M D Armour F F a d Gu tavson R G Plumag and Oviduct Respons to Female Hormon in Fowls Endocrinology **14** 349 354 1930

[6] *Cr nwoo l A W an l Blyth J S S Diag osi of F tal Pregnancy Proc Roy Soc* London S B **16** 247 257 1934

[11] Mit h ll J B Jr Action of Theeli o th Domestic Fowl Proc Soc Exp r Biol & Med **30** 500 1933

[1 8] Hu C K a d Frazi r C N Effect of Ovary and of Urinary Estrog on Growth f Hair in Rabbit Anat Rec **77** 155 161 1940

[1 1] Quinn J P and Burrows W H Effects of F male Sex Hormone on Plumag Color J H red **26** 299 303 1935

[1 2] Greenwood and Blyth Variation in Plumag Respon e of Brown Legho n Capo to F tro Proc Roy Soc London s B **118** 97 132 1935

[142] Fr ud J On the Biological Tests of th F male S ual Hormon Menformo Influence on Feathers Ber ges Phy iol **67** 371 1932

[1 2] Bloch Br an l Schrafl A Experim nt lle Unt rsuchu gen über d n Einflu des Ovarial Hormons auf di Pigm tbildung Arch f D mat u Syph **165** 268 273 1932

Ovarian Insufficiency

In *aplasia* of the ovaries the pubic and axillary hair is sparse or lacking The rest of the hair has in some cases been seen to be underdeveloped [14.3, 14.5]

In B Bloch's[14.5] case juvenile cataract and poikiloderma were present

Primary ovarian insufficiency may lead to a habitus with overlong extremities and also to dwarfism [13.18, 14.6] The syndrome of primary ovarian insufficiency is characterized by excessive amounts of urinary follicle stimulating hormone and low levels of 17 ketosteroids There is lack of breast and uterine development and other symptoms of infantilism The axillary and pubic hair is scanty but not absent Albright and his coworkers believe that the growth of the axillary and pubic hair in females is not stimulated by the ovary but by an adrenal cortical hormone (see chapter on Puberty) Melanoderma and mild depressive psychosis in ovarian deficiency have been described by S Block[14.7] and later by Bonilla[14.8] and Marañon (after Bonilla[14.8])

Naturally a great amount of information is available on the female *castrate* The cutaneous symptoms after castration of the adult female are essentially those of the menopause However it should be emphasized that castration of the woman does not always change her appearance

Secondary ovarian hypofunction clinically characterized by amenorrhea or irregularity of the rhythm and amount of the menstrual flow usually does not cause dermadromes though hypertrichosis is frequently encountered [14.9, 14.31] The hypertrichosis may disappear with the restoration of a normal ovarian function It seems that hypertrichosis in ovarian hypofunction is due to the relative weakness of the prohibiting effect of the estrogen Such an imbalance may be caused by ovarian deficiency as well as by adrenal cortical hyperfunction The urinary excretion of 17 ketosteroids has in many instances of hypertrichosis been found above the normal level [14.32, 14.33] Application of estradiol salve and intradermal injections of progynon are able to make the local hair growth disappear[14.34] but the effect cannot be relied upon The administration of stilbestrol in primary

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[14.2] Bloch B Poikiloderma atrophicans mit Mangel der Ovarien Literus t ophie Juveniler Katarakt u Lebere r gha k it d Parasympathicu Schweiz med Wchnschr 56 753 7 6 1926

[14.3] Olivet J Über den angeborenen Mangel beider Eierstöcke Kastration und Behaarung Frankfurt Ztschr f Path 29 477-401 19 3

[14.5] Goldwasser J Ein Fall von Aplasia ovariorum mit pluriglandulär Dysfunktion und mit durch Transplantation von Ovarium behobener Amenorrhoe Arch f Gynäk 153 166 1933

[14.6] Varney R F Kenyon A T and Koch F C Ovarian Dwarfism J Clin Endocrin 2 137 145 1942

[14.7] Block S A New Syndrome M Rec 90 984 1916

[14.8] Bonilla E Insuffisance ovarienne mél od mi et troubles psychiques Rev franç d endocri 1 3 408-4 6 19 5

[14.9] Solowij w Th Hypertrichose bei Frauen Arch f Frauenk 13 155 1927

[14.30] Lisser H Feminization and Demasculinization of a 17 Year-Old Girl by Injection of Stilbestrol Endocrinology 27 355 1940

Strassmann F O Endocrin Treatment of Masculine Hair Growth Associated With Menstrual Disorders in Women J Internat Coll Surgeon 4 137 14 1941

Hamblen E C Cuyler W K and Baptist M Urinary Excretion of 17 Ketosteroids in Ovarian Failure in Hirsutism and Virilizing Syndromes J Clin Endocrinol 1 763 7 1 1941

[14.33] Greene R Androgen and Pregnandiol Excretion in Hypertrichosis Lancet 2 486-487 1940

[14.34] Mussio-Fournier J C and Albrieux A Absorption of Sex Hormones by Skin Case of Facial Hypertrichosis Improved by Intradermal Injections of Estrogen Presse méd 48 569 5 0 1940

amenorrhea is often followed by hyperpigmentation of the linea alba and nipples[1435] This was not observed in the stilbestrol treatment of menopausal complaints

Ovarian Tumors

Cysts and teratomas rarely cause dermadromes except those connected with hypoovarism Granulosa cell tumors in children may cause precocious puberty[1436] but there do not seem to be skin manifestations in adult patients

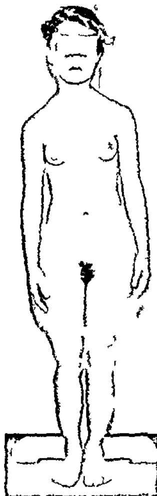


Fig 195 Precocious puberty Female aged 6 years Removal of ovarian tumor at age of [illegible] years Premature development started at 3 Cervix and uterus of adult size Bone age 13½ years (Courtesy Wisconsin General Hospital)

[1435] Davis M E Boynton M W Ferguson J H and Rothman S Studies on Pigmentation of Endocrine Origin J Endocrinology 5 138 194[illegible]

[1436] Meyer R Some Species of Ovarian Tumors and Their Relations to Sex Characteristics Am J Obst & Gynec 22 69[illegible] 1931

Dysgerminoma[1436] or seminoma ovarii is rare This type of neoplasm has been observed in pseudohermaphroditic individuals The external genitalia are infantile These tumors which usually occur in the second and third decades do not masculinize the patient [1436]

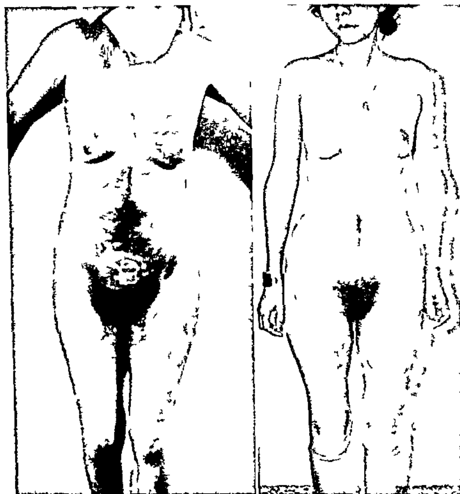


Fig 190 Masculi i i g o ria tumo before and aft r operatio (Fr m Bla kmun R I Am J Ob t & Gynec)

Arrhenoblastomas cause defeminization and masculinization Baldness of the masculine type may develop characteristic deposits of fat may vanish the breasts the other ovary and the uterus may atrophy and amenorrhea may ensue There is enlargement of the clitoris atrophy of the labia majora and marked hirsutism of the male type with beard growth The symptoms are reversible by successful operation The tumors arise from the seminiferous tubules in the hilus ovarii or from a primitive ovotestis The histologic picture

shows adenomatous structures resembling seminal tubules and/or epithelial cords The endocrine testicular function accounts for the deep biological changes[1436 1441]

In *Carcinoma*[144] *Luteoma*[1443 1445] *Sarcoma*[1446] and *Hypernephroma*[1447] masculinizing features have been described in rare instances Kepler[1343] observed



Fig 197 — Female aged 20 years Facial hypertrichoses in ovarian tumor of unknown pathology

Cushing s syndrome in a case of adrenal like tumor of the ovary There was excessive excretion of 17 ketosteroids but a normal urinary output of estrogens In rare instances[1449] diffuse erythematous edema of the skin has been observed as a peculiar form of metastases from ovarian carcinoma (see chapter neoplasms)

[1437] McIntyr W K Arrh noblastoma J Obst & Gynaec Brit Emp 49 41 50 194?
[14?] edli F Ceschlechtsumstimmu g durch Ovarialtumor (Arrhenoblastoma) Arch f Gynäk 149 ? 3 ?36 193
[?4] Mathias E Ope ativ ntf ntes Arrhenoblastom mit spät r r Schwang rschaft Zbl f Gyn 57 449 4 5 1933
[1440] Norris F H Arrh noblastoma Am J Canc r 32 1-39 1938
Liss r H Taime A and Morton D G Arrh noblastoma R moval Followed by R feminization and Pr gn ncy Clinics 1 768 781 1942
[?] Esau F limakt risch Gesicht behaaru g Klin Wchnschr 8 16 0 1671 19 ?
[1 4?] Blackmun R L Tumor With Masculinizing Syndrome Am J Obst & Gynec 42 1036 1041 194
[1] Cosacesco A Draga esco S Georgescu M and Dinischiotu G T Lutéi m d l ovaire contribution anatomo-cli iqu à l étud du virilism ovari n P es e méd 39 1 01 1 07 1031
[?] Mayer J Mascull i i g Luteoma V1 hows Arch f path Anat 309 6 -613 1942
[?] Col lberg Mischgeschwul t des Ovarium (knorpelhaltiges Sarkom) männlich B haarung Stimmv rän lerung und Klitorishypertrophie Zbl 52 1162 1164 1028
[1 ?] Trol kij V Hirsuti mu d Ovarialtumor H ilung d Entf rnu g d r Geschwul t Vrač D lo 12 1115 1929 Zbl 31 460
[1449] Urbach F Waldow J a d Stamm C J Diffu e Cutaneou M tastatic Lesion From an Ovarian Carcinoma Arch D rmat & Syph 42 06 970 1041

Small blue *Angiomas Papillomas* and *Fibromas* in large numbers may occasionally accompany tumors of the female sexual organs[1449] Such benign growths of the skin are seen in the menopause as well as in pregnancy and ab dominal diseases

Ovarian Relationship of Dermatoses—In the light races women are supposed to be more often brunette than men[1450] New investigations seem necessary The preponderance of the female sex in some dermatoses is well known Examples are hemangioma lupus erythematosus lupus vulgaris and some other types of skin tuberculosis scleroderma Raynaud s disea e chloasma acrodermatitis atrophican some circumscribed keratoses[14 1] urticaria pityria is rosea eczema impetigo herpetiformis erythrocyanosis cruris erythema nodosum Paget s disease of the nipple tinea versicolor[667 145] *

In order to accept the ovarian etiology in a given dermatosis the claimed re lationship should be supported by menstrual or menopausal coincidence dis appearance in pregnancy cure by hormonal therapy cure by castration after failure of other therapy and by other evidence of gonadal character The literature of the last fifty years abounds with such reports[14 3 14 5] However no dermatosis has been described which by its morphological picture alone would invariably permit the diagnosis of an ovarian dysfunction or di ea e

Cases of Purpura[1456 1458] psoriasis[1459 1460] keratoderma palmare and plan tare[1461 146] erythema perstans[1463] rosacea urticaria and angioneurotic edema

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* Men are more subje t to the following dermatoses lich n ofuloso um lichen planu p derm phytosis inguinalis K posi s hemo hagic pigmentary sarcoma anc r of the lower lip and mouth an l s me oth rs

[14 9] Freund H W Haut b l sch a g r n u g nitalkrank n Frau A ch f D rmat u Syph 47 410 1898

[1 50] Hav lok Ellis Mann und W ib Würzburg 1909 Cu t Kabitz ch

[145] No ak J B zi hungen zwischen Haut und we blich m G nital Bi logi und Path logi des Weib es vol V 3 B rlin 19 7 Urban & Schwar nb e g

[1452] Alle i E V The Relationship of Sex to Diseas A n I t Med 7 1000-1012 1934

[1453] Scheue O Hautkrankheit n s uell n Ursprungs bei F auen B lin 1911 Urban & Schwar enberk

[1454] Puhl Menstruelle Hauters h i ung Dermat Wchnschr 54 581 191

[1455] Wi ne I Di Be i hu gen d r G nitalorgane zu Hautveränderu gen Hall a S 19 4 Carl Marhold

[1456] C s llo C A Sob púrpura o árica Rev ud am de en io rinol 21 76 784 1938

[1457] Urbach E F lok in bedingt jah z hntela g bestehe de Purpu a Zbl 42 164 193 1933

[1458] h eld G H V be konstitution ll m n tru lle rheumatoi le Purpura Folia ha mat 38 418-421 19 9

[145] Vogt F Pso iasi u d Ovarialfu ktion Monatschr f G burtsh u Gynäk 81 28 88 19 9

[14] Li n tti G Psoriati Arthropathy in Wom n Whos Ovari Ha Been R m ed Opo th rapy Folicli Po (z p at i 45 1606 1610 1938

[14] B tto-Micca A Su di u caso di heratodermia simm tri a palmar plant in d a am orroica guarita on p parati opot rapici Riv d ost t e ginec prat 12 1 1930 Zl 34 4 9

[14] M kai T and Shibata S K ratod rmiatylodes palmari progr ssiva A ta l rm tol Japo 14 653 669 19 9

[1463] Matusi I and Fajngol l A Eryth ma perstan und das en lokri Sy t m Odess med J 2 607 19 8 Zbl 31 07

(see menopause)[1464, 1465] alopecia areata[1466, 1467] eczema[1467, 1471] prurigo dermatitis herpetiformis[147] parapsoriasis[14 3] pruritus[1474] and many other dermatoses have thus been linked to ovarian dysfunction Bohnstedt[1475] found the urinary excretion of pituitary gonadotropic hormone increased in rosacea and dermatitis dysmenorrhea symmetrica Chloasma in nonpregnant women and other pigmentations are in some cases of ovarian origin[1476] They have *occasionally been cured by local application of strong estrogen salve*[1477]

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146 Sáinz de Aja E A Urticaria pigmentosa akutes Quincke sches Oedem und Neurodermitis geheilt d Thyroid u Ovariumtherapie Actas dermo sif **22** 473-474 1930 Zbl **36** 77

1465 Blach S Durch endokrine Störungen bedingte Urticaria Deutsche med Wchnschr **56** 184 195 1930

1466 Říhová V Alopecia areata und Ovarialstörungen Česká dermat Šamberger Festschr pp 530 534 1931 Zbl **44** 43

1467 Garnier G Eczema Due to Estrogen Lutein Disequilibrium 2 Cases Bull Soc franç de dermat et syph **46** 319 327 1939

1468 *Desaux A À propos de la communication de M Georges Garnier sur l eczéma par le déséquilibre* hormonal folliculino-lutéinique Bull Soc franç de dermat et syph **46** 627-630 1939

1469 Berger M Dermatologische Beziehungen einzelner Frauenkrankheiten endokrine i Ursprungs Schweiz med Wchnschr **65** 36 367 1935

1470 Urbach E Endokrin bedingte Haut Schleimhaut und Haarerkrankungen Arch f Dermat u Syph **161** 492 503 1930

1 71 Szego P Ekzem mit Ovarialstörungen Gyógyászat **68** 306 19?8 Zbl **27** 788

1472 Riecke E Dermatitis herpetiformis Handb d H u Gk **7** 2 612 1931

1473 Cartia B Un caso di parapsoriasi lichenoide condismenorrea guarito con la cura opoterapica Gio ital di dermat e sif **69** 1423 1437 19_8

1 7 Leszczyński R von and Liebha t S Hormonale Frauendermatos n I Ueb r [illegible] präklimakterische und klimakt ische Hautreaktionen Dermat Wchnschr **93** 1289 130 1931

1475 Bohnstedt R M Untersuchungen über Ausscheidung von Prola i A und Follikulin im Harn von Hautkranken Klin Wchnschr **13** 1675 167 1934

1476 Schölzke K H Chloasma uterinum in nonpregnant women Med Welt **13** 1413 1414 1939

1477 Rocca F Estrogenic Substances in Treatment of Chloasma J Clin Endocrinol **2** 217 18 194?

CHAPTER XXI

PUBERTY

Puberty is the transition from childhood to adult age seen mainly from the viewpoint of sexual maturing In the female sexual maturing means the establishment of regular menstruation In the male emission of semen must be considered the beginning of sexual maturity but this event is much less sharply accentuated and usually forgotten in adult life Around the beginning of the production of mature gametes is grouped the development of the *secondary sex characters* Furthermore puberty is a period of intensified organic growth and reorganization which affects almost every part of the body Finally it is a period of psychic and intellectual ripening and adjustment The onset of menstruation is but little speeded up by such factors as race and warmer climate probably more by urban life better living conditions and psychological factors [1478] In the United States the menarche starts between twelve and fifteen years most frequently at 13 9 (Engelmann after Novak[1478]) compared with 15 5 in the corresponding zone in Europe

Dermadromes of Puberty —The establishment of the cycle follows within a year, the growth of the pubic and axillary hair The subcutaneous fat padding gradually smoothens and rounds the skeletal and muscular contours Typical fat accumulations are found in girls on the cheeks shoulders breasts buttocks lower abdomen mons veneris and thighs [1479] Girls develop less pigment than boys Neurath[1479] considers little bunches of veins in the skin of the thighs to be a female sex characteristic In boys a palpable sometimes tender subareolar node of mammary gland tissue often appears at the onset of puberty and disappears at the end Temporary gynecomastia in boys is seen occasionally [1480]

The *apocrine glands* start their secretion at puberty earlier in girls than in boys These glands represent a type of skin gland which is in close relationship to the gonads The apocrine glands are sweat glands which develop from the hair follicles and open into the hair follicles which the ordinary sweat glands the so-called small or eccrine glands never do They do not secrete sweat but give off a secretion consisting of particles of the secreting cell protoplasm Thus their type of secretion places them between the sebaceous and the sweat glands many authors consider the apocrine glands to be a rudiment of the scent glands of many mammals Such glands are known to have a close relationship to the sexual life The peculiar odor of the human axilla which is different from the

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[1478] Novak F Menstruation and Its Disorders New York 1931 D Appleton & Co

[1479] Neurath R Physiology and Pathology of Puberty In von Pfaundler Schlossmann The Diseases of Children vol I Philadelphia 1935 J B Lippincott Co pp 503-526

[1480] Jung F T and Shafton A L Mastitis Mazoplasia Mastalgia and Gynecomastia in Normal Adolescent Males Illinois M J 73 115-123 1938

odor of sweat may be due to the chemical characteristics of the apocrine glands which contain iron fat and cholesterol in remarkable amounts [1451]

In man the apocrine glands are most densely *grouped in a heavy organlike* layer in the center of the axillary fossa Less concentrated groups occur in the pubic area particularly in the mons veneris and also around the anus in the areola mammillae (Montgomery s glands) and in the external ear ducts [145] The thick layer of apocrine glands in the axilla is practically nonexistent in childhood It is more pronounced *in the female and much more developed in the Negro than in the white man* [1453] It develops early *in puberty* It is discernible several years before the onset of menstruation [148, 1454, 1455] Some relationship to menstruation pregnancy and lactation has been claimed [1453] but the matter is still controversial Fox Fordyce disease is a chronic inflammatory condition of the apocrine glands (See Fox Fordyce disease) The axillary concentration of the apocrine glands atrophies slowly *in the menopause*

The sweat glands especially those of the hands are often remarkably active during puberty

The activity of the sebaceous glands is stimulated in puberty This fact together with the keratosis of the follicular opening results in seborrhea and in the formation of comedones and acne Comedones must be considered a physiological development of puberty *since they can be found in almost every adolescent*

In childhood there are no differences in length abundance diameter and distribution of the *hair* The sexual characteristics of the hair develop during puberty At first there is no noticeable difference in the shape of the escutcheon of the two sexes

After the seventeenth year the *male* pubic hair extends in a triangle along the midline toward the navel while the female escutcheon has a sharp *horizontal* upper border line This however is not always the case About one out of eight men has a female distribution of the hair often connected with subnormal beard growth and *other feminine stigmata* [1456] *The lack of vigorous pubic hair* growth is generally considered a stigma of infantilism The lanugo in the male is coarser often pigmented especially on the chest the arms the legs on the perineum and around the anus The hairs in the nostrils and ears tend to become coarser in later years The hairiness in males can reach very embarrassing degrees

The pubic and facial hair in the *female* is probably stimulated by the adrenals rather than by the gonads since the axillary and pubic hair is not completely absent in the primary ovarian failure (ovarian dwarfism) It appears at puberty when the excretion of 17 ketosteroids rises probably due to adrenal cortical activity

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[1451] Richter R Anat mie fe apok ta n Hautdrü n des M n h n mit besond B rü k I htl gung des Arb Ihihl o gar Vf hon Ar h f path Anat 287 7 200 193

[1452] Linku F No n al A at mi der Haut Ha dl d H u Gk I I I 369 19 7

[1453] Tappeine S Diagn si of Acanthosis Rubra Lich noides and of Fox Ford e Di se Dermat Wchnsch 107 14\ 1488 1938

[1454] Kyrl T Hi tol iologi l Haut ll lin 19 Julius Sp inge r

[1455] Klaar J Da w ll ll b Axillarorgan t im M nsch n Wien klin W hnschr 39 127 131 19 6

[1456] Risak F I I lie rschiedl n n Art n d r männli hen G nitalb haarung Ztschr f Konstitutionsl 15 163 176 1931

The prepuberty male castrates develop slightly less pubic and axillary hair than normal females Oophorectomized females do not lose their body hair however it falls out in Simmonds disease Addison s disease myxedema and very old age In all these conditions the excretion of 17 ketosteroids is very low [1318] The axillary hair also disappears in hepatic cirrhosis (see cirrhosis)



Fig 198 —Male distribution sternal patch of hair No othe endocri at normaliti s

Girls of course are supposed to have a smooth skin without noticeable hair except in the pubes and in the armpits But quite often considerable hair growth along the legs arms on the upper lip and even in the sternal region of the chest can be seen without any detectable endocrine abnormalities This tendency is more pronounced in some pigmented races e g the mediterranean [13 5 1487] A peculiar accumulation of long pigmented hairs is not infrequently found around the female nipples although it is rarely seen in men

During adolescence the *hairline* which is the border of the scalp hair acquires its characteristic configuration The fairly straight frontotemporal hairline of children develops in boys a more or less marked triangular hairle s notch which points in the direction of the vertex where the male baldness will develop later According to R O Stein[1493] who described this calvities frontalis adolescentium it is not observed in castrates nor in eunuchoids nor in women except in mas culinizing conditions This rule has not too many exceptions The calvities frontotemporalis is seen in the vast majority of the men and in only less than 6 per cent of the women (Maranon after Mu sio Fournier[15])

While the male hair in front of the ears unnoticeably merges into the beard sideburns are seen only in women who have other symptoms of hirsutism Marañon (after Mussio Fournier[15]) sees a sexual difference in the hairlines of the nape of the neck In the female the borderline is distinct and shows two lateral prolongations and sometimes a medial one consisting of strong hairs In the

[1487] Fried nthal H Das Haa kleil des Mensch n Jena 1908
[1493] t in R O Funu b idi mus Zt l 18 570 19 6

male the transition from the head hair into the lanugo of the nape of the neck is more gradual This characteristic is not very pronounced The male *eye brows* are thicker longer and less regularly implanted They have a greater

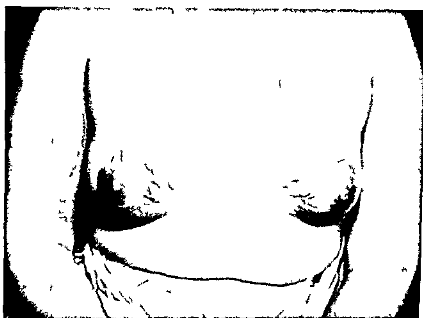


Fig 199 —Hyp rtrichosis of breats The patie it is ol ese has a strong facial hair growth a l a decil dly ma culine hairline No d finite endocrine disturl anc coul l l found Th 17 k to terol l xcretion was normal [illegible]

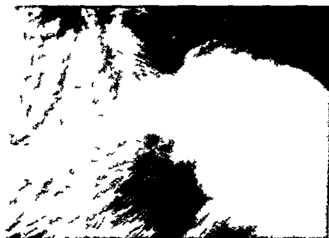


Fig 00 —Female aged 30 year Calvities temporall in the sam pati nt a shown in Fig 199

tendency to grow together on the glabella The development of the eyebrows in the male parallels the general hairiness In middle age some very long hairs appear in the eyebrows In some men the eyebrows take on a bushy appearance

which is never observed in women. The *eyelashes* are stronger, longer and more curved in women than in men.

Shaving usually becomes necessary between the ages of sixteen and seventeen. At first, the rate of *beard* growth is very slow, requiring shaving only once a month or less. Marañon (after Mussio Fournier[15]) distinguishes a period of juvenile beard growth on the lateral upper lip, zygomatic, chin and submaxillary regions from the mature beard which forms by coalescence of the growth centers.

The color of the hair often deepens during puberty, particularly from sixteen to nineteen. This may be due to increased oiliness or to increased pigmentation (Breipohl after Jung[1489]). The latter is true if there is a hereditary factor of pigmentation which had not yet become manifest. Blond Jewish children often darken considerably in this age.

Certain strands of elastic fibers in the skin of the face which have been described under the name of *elastica mimica* develop at puberty and degenerate



Fig. 201. Striae not related to pregnancy, ascribed to loss of weight. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

slowly after the age of forty.[1490] *Striae* distensae occur frequently in both sexes during adolescence. They are common in the skin of the lower back, across the thighs, above the patellae and on the upper arms. They usually run transversely to the length of the body or of the limbs in symmetrical, rarely unilateral arrangement. In the lower back they are typically found in parallel lines below

[1489] Jung, F. T.: The Physiological Changes Incident to Puberty. Illinois M. J. 80: 477–494, 1941.
[1490] Vohwinkel, K. H.: Ueber die Altersveränderungen des Hautbindegewebes und über die sogenannte Elastica mimica bei verschiedenen Rassen. Dermat. Ztschr. 62: 95–104, 1931.

the twelfth dorsal vertebra sometimes occupying almost the whole width of the back down to the center of the sacral area Their[149] appearance often coincides with growing pains in the limbs The distribution of the striae in puberty suggests a mechanical factor But it is likely that a toxin which weakens the elastic fibers plays a part Some authors consider the appearance of striae in infectious diseases an ominous sign but there is little foundation for this belief (See striae in chapter on pregnancy)

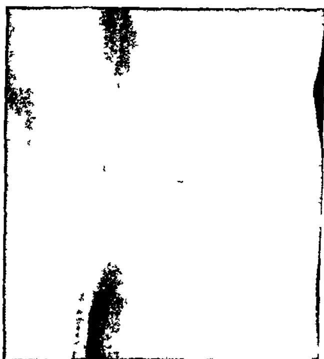


Fig 202 — Male aged 1 years Striae of adolescence

True *precocious puberty* is the phenomenon of early sexual maturity apparently not due to endocrine or cerebral disease but to unknown constitutional possibly hereditary factors This constitutional type without endocrine tumor occurs in girls and is probably the most frequent variety of precocious sexual development[150] The advanced development in these cases sometimes starts during intrauterine life Menstruation without accompanying gross endocrine disease is known to occur several years before the normal time of onset

All the sequences of puberty are hastened including the changes in skin and hair The dermatologic aspect of early maturity is discussed in the chapter dealing with adrenal cortical tumors which are frequently responsible

[149] Petges G Vergetures de croissance ou des adolescents Nouv Pratique Dermat Pelgique vol VI Paris 1936 Masson & Cie p 55

[150] Nowak F The Constitutional Type of Female Precocious Puberty 9 Cases Am J Obst & Gynec 47 70-41 1944

Almost identical syndromes of precocious puberty can be caused by anterior pituitary hyperfunction by pinealomas[1493] and other cerebral conditions of hetero geneous etiology[1494] The latter include tumors (glioma) of the corpora mammil laria hypothalamus[1495] and other regions brain abscesses tuberous sclerosis[1496] and encephalitis lethargica[1497] Precocity is also a part of Albright s syndrome (see there) It furthermore occurs in some conditions of the ovaries such as hyperovarism[1498] ovarian cysts[1498] arrhenoblastoma teratoma[1499] and granulo a cell tumors Precocious puberty is a characteristic of hyperorchism caused by neoplasms arising from the endocrinal (interstitial) part of the testis

Delayed puberty is seen in connection with hypopituitarism hypogonadism and hypothyroidism In gonadal deficiency the thymus is usually persistent[1298]

Skin Diseases of Puberty

Acne vulgaris is surely the most important and common dermatosis of the puberty age Pollitzer[1500] in 1914 gave its incidence in the United States as 7 5 per cent of all dermatoses but it seems even more common today There *is hardly a boy or girl who is not at some time and in some degree afflicted with it* It is almost a physiological disease

Follicular keratosis comedo formation and seborrhea are the primary lesions of acne Inflammation of acute or chronic character with or without abscesses and finally healing with a scar is the sequence of secondary symptoms The face back and the sternal region are most commonly involved The micro scopic examination of early lesions shows a follicular keratosis and epithelial atrophy accompanied by loss of the finer elastic fibrils near the epithelial wall[1501] This latter fact may account for the open pores

Gonads Age Sex—The most obvious relations exist with the gonads Acne is extremely rare in early childhood although it has been seen before the age of one year especially in males[150] [1504] From five to eleven years the inci dence curve rises slowly without severe cases Then it soars distinctly coinciding with the appearance of pubic and axillary hair the development of the breasts

[1493] Bing J F Globus J H and Simon H Pubertas P aecox Pin aloma J Mt Sinai Hosp 4 935 1938

[1494] Casrella P La pub rtà precoc nelle cerebropatie infantili Rass gna di studi psichiat 24 855-896 1935

[1495] Weinberger L M and Grant F C Precocious Puberty and Tumors of th Hypothalamus Arch Int Med 67 6? 1941

[1496] Cornil L and Kis I P Macrogénitosomi précoc Arrk ation mong loid Ad nom s sébacés du visage Re n urol 1 86 88 1930

[1497] Ford F R a d Guild H Precocious Pub rty Following M asles Enc phalomyelitis and Epidemic F cephalitis R latio *of Intracranial Tum rs and I flammato y Proces to th Sydnrome* of Macrogenitosomia Praecox Bull John Hopkins Ho p 60 19 03 1937

[1498] Z d l Z dau M Fall vo vo zeitige Geschlecht reife Novy khir arkh. 15 510 19 8 211 31 331

[1499] Si gmund H Pubertas praecox als Folge chorion pithellom t3 er Wuc eru g n Arch f Gynäk 149 495 514 193

[1500] Pollitzer S Acne Vulgaris J Cutan Dis 32 312 1914

[1501] Lyn h F W Acne Vulga i Hi tologi Cha ges f Farly Lesions Arch De mat & Syph 42 593 1940

[1502] Ja n J J Infantile Acn Vulgari J Pediat 20 365-367 191

[1503] Gray A M H Acn in a Child Aged ? Y rs Proc Roy Soc Med 27 9 1934

[1504] Aitken R Acn in Inf t Brit J D mat 54 ? 2 ?73 191

and the onset of the menses[1505] Girls develop acne earlier in life At the age of seventeen almost every boy or girl has some though often inconspicuous blackheads or pimples The severe cases are seen in girls from fourteen to sixteen in boys between sixteen and nineteen[1506] Boys have a little higher morbidity and show severe cases more often This has been shown in investigations of many thousands of adolescents in various countries[1505 1507]

Some statistics give a lower incidence but it seems that they only take into account the more severely inflammatory cases After the age of twenty acne becomes less and less frequent but there is no sharp upper age limit Even in the fourth decade acne is not uncommon in men and exacerbations in women at the onset of and even after the menopause occur There does not seem to be acne vulgaris in the aged

Next to the coincidence of acne with the onset of puberty the time relationship to menstruation suggests a gonadal factor It is common knowledge and it has often been confirmed by medical observation that acne exacerbates before during or after the menses the individual case usually remaining constant to type with regard to the time relation of the exacerbation[1508] The intermenstrual remission is often complete However similar menstrual flare ups can be seen in lupus erythematosus psoriasis rosacea eczema[1455 1509] and other chronic dermatoses Therefore the menstrual exacerbation itself is a weak argument for the gonadal cause more so since it occurs in only a certain percentage which varies from about 30 to 75 per cent in several observed series of girls Menstrual disorders and hypogonadism are no more frequent in girls with acne than in those without acne[1501 1506 1510 1511]

A great deal of work with modern methods has been done in order to find better proof of an imbalance of hormones in juvenile acne than is furnished by statistical and clinical methods This work showed that in patients with acne the output of estrogen in the urine is below the normal level Rosenthal and Kurzrok[1512] and later Rosenthal and Neustaedter[1513] were unable to find any estrin in twenty seven out of thirty four young women with acne These low urinary estrogen contents in patients with acne were confirmed by a number of authors

In men with acne the excretion of estrogen was also found to be well below normal On the other hand the output of androgen in men was found to be higher in acne patients while it was found in normal level in women Only Cornbleet and Barnes[1514] found the daily urinary androgen output in male and female

[1505] Bloch B Zur Pathogenese der Acne vulgaris Zbl **44** 519
[1506] Hinrichs n J and Ivy A C Incidence in Chicago Region of Acne Vulgari Arch Dermat & Syph **37** 975 98? 1938
[1507] Schwartzman J Abnormalities (Adolescence) J Pediat **21** 03 10 194
[1508] Urbach F and Schiller W Der heutige Stand des Akneproblems Akne sexualis Med Klin **33** 1 01 1703 1937
[1509] Cohen E L Incidence of Clinical Acne in Men Lancet **1** 168 194
[1510] Bach E Über die Behandlung der Acne zu Allg meinerk a kung DL Bern 1907
[1511] Cunningham R L and Lunsford C J Acne Related Causes California & West Med **35** ?? 26 1931
[1512] Rosenthal T and Kurzrok R F ction of Estrin in Acne Proc Soc Exper Biol & Med **30** 1150-1151 1933
[1513] Rosenthal T and Neustaedter T Estrogenic Substance in the Blood of Patients With Acne Arch Dermat & Syph **32** 560-56? 193
[1514] Cornbleet T and Barnes B The Hormones and Acne Vulgaris Arch Dermat & Syph **40** 249 ?5 1939

patients with acne a low normal Wile[1515] and his collaborators impressed by the relatively high and unchanging androgen findings believe that the ratio between urinary androgen and estrogen is of great significance They found its value in acne much higher about double of the normal figures These observations have essentially been confirmed [1516 1517]

The excretion of sex hormones in the pre acne age of less than eight is very small and the same for both hormones in both sexes From eight to eleven both steroid sex hormones ri e the androgen quicker in the male the estrogen quicker in the female When adulthood is achieved the normal characteristic ratio of the excreted sex hormones is established [1518] Acne is characteristic for the years of transition when the ratio is changing just as it is characteristic for the catamenia At this point of the menstrual cycle the urinary output of estrogens has reached its lowest level [1519 15 0] The androgens excreted by the woman do not fluctuate with the cycle so that a relative preponderance of androgens exists at and around menstrual time when acne is well known to exacerbate There is much evidence that male eunuchoids do not have spontaneous seborrhea and acne [1372] but may acquire it during treatment with androgenic preparations just as women and also men often do under treatment with testosterone propionate [15-1] It is noteworthy that acne produced in eunuchoids by injection of testosterone propionate disappeared on withdrawal and reappeared on resumption of the injections [15] Boys generally have an increasing incidence of acne from seventeen to twenty one years and their cases are often more severe with a greater tendency to pyogenic infection and involvement of the trunk [1501] It is a general impression that virile boys are more likely to show acne than those of a more feminine type [1 98] and also that girls with severe acne are of less marked feminity The occurrence of acne in masculinizing tumors of the adrenals the pituitary and the ovaries has often been observed Zimmer[15 3] found gynecomastia more often together with acne than with normal skin but his series is small

Long before it was possible to prove any changes in the level of sex hormones the attempt had been made to cure acne with organ extracts which in the light of our present knowledge probably had very little potency Later a great number of investigations were made with preparations of undoubted potency Anterior pituitary like gonadotropic hormone prepared from urine of pregnant women has been tried by scores of authors While most of them found little or no

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[15 5] Wile U I Snow J S and Bradl ury J T Se Hormones in A ne Arch Dermat & Syph 39 200- 10 1939

[1 6] Lawrence C H and W thess n N T Endocri Dyscr ia of A ne in Wom n Endocrinology 27 755-758 1940

Lawrence C H and Werthessen N T Acne in F males Internat Clin 1 198 05 1942

Nathanson J T Town L E and Aub J C Sex Ho mo es i Urin and Acn Endorinology 28 851 1941

Smith O W a d mith O W Urinary Excretion of E trog nic a d Gonadot opic Ho mones Du ing Menstrual Cy les Period of Conception nd Early Pr gnan y N w E gland J Med 215 908 1936

[1520] Di g man F and Laqu u F Ned T tijdschr v g neesk 84 3 87 1940

[2] C i t S H Salmon U J Caines J A and Walt r R I Bi logi Eff ct of And og (Testost ron Propi onate) i Women J A M A 114 1539 1544 1940

[1372] Hamilton J B Treatm nt of S xu l Und rde lopment With Synth ti M le Hormone Sub tance Endoc inology 21 649-654 193

[15] Zimm r E Cy ikomastl und A n vulgaris Diss Erlangen 1935

value some claimed benefit [15 4] Just as variable were the results with estrogens but it seems that good results outweigh the poor results though not very impressively B Zondek[15 5] showed that follicular hormones can produce estrus



Fig 203 The familial t d y to acne Father and son *Below* mother and daughter

phenomena if applied percutaneously This has since been shown in many experiments The practical application of this observation in the treatment of acne by ointments containing estrogens and androgens has mostly been disappointing

[4] Lawrence C H The Anterior Pituitary Hormone A Clinical Study of It Effect in Acne Vulgaris J A M A 106 983 987 1936

[5] Zondek B Local Treatm nt of Acn With E t og n Schweiz med Wchnschr 65 1168-1169 193

Luteal hormones have been recommended but have had little trial compared with estrogens The alternating use of large doses of estrogens during the first ten days following the menses and luteal hormone on five consecutive days during the third week of the cycle was followed by lasting improvement in five girls after three months of treatment (Urbach and Schiller[1505]) Considering the fluctuating course of acne a sceptical attitude toward all reports of small numbers of cases is justified Androgens have been tried in the treatment of acne in spite of the many experiences with their acnegenic effects The reports are overwhelmingly discouraging In several experimental series[1514 1516] controls received injections of bland sesame oil The effects were about just as good as with androgen in sesame oil—and both were not too poor In summarizing the gonadal relationship of acne one is permitted to say that the age incidence menstrual accentuation occurrence in masculinizing tumors nonoccurrence in male eunuchoids urinary and blood content of sex hormones and the production of acne with androgen injections proves its existence However the degree of our knowledge of the mechanisms involved has not yet yielded a reliable method of hormonal therapy This opinion is reflected in a symposium on acne of leading American dermatologists Not one out of five dermatologists used hormonal therapy to a larger extent than as an adjuvant [1517]

Hypertrichosis in girls with or without other signs of endocrine disturbance usually causes a great deal of anxiety The patients or more often the parents soon become worried about the possibility of serious pituitary or adrenal disease After investigation this question is fortunately most often answered in the negative But then the cosmetic problem remains It is beyond the scope of this book to deal with the treatment of hypertrichosis But it may be mentioned that endocrine therapy so far has only been successful if other endocrine symptoms especially amenorrhea were present

The *outbreak* at puberty of *chronic dermatoses* like psoriasis lupus erythematosus and epidermolysis bullosa has been observed sufficiently often to make coincidence unlikely [1445] In Recklinghausen s neurofibromatosis the number of tumors existing from early childhood may suddenly increase so that the fully developed syndrome results Onset of lipoma formation in puberty has become known in Dercum s disease It seems correct that in adolescence the tendency to keloid formation is more marked than before A keratosis involving the volar surfaces of the fingers of Japanese girls and mostly starting after the first menstruation has been described by Dohi and Miyake under the name of keratodermia tylodes palmaris progressiva Takesita[1518] reported 217 cases seen in ten years and Kwabe[1519] 50 cases [1520] Dysmenorrhea and increased basal metabolism have frequently been observed It seems that besides gonadal factors

[1516] Moll, H M Treatment of Acne Vulgaris With Testosterone Propionate Endocrinology 23 603 1938

[1517] Symposium on Practical Management of Acne Vulgaris J Invest Dermat 3 143 1 7 1940

[1518] Takesita S Keratodermia tylodes palmaris progressiva Hitu to-Hitu yo 5 93 1937 Zbl 57 606

[1519] Kwabe M Di sogenannte Keratodermia tylodes palmaris progressiva Jap J Dermat & Urol 34 1 1 1933

[1520] Kitamura S Keratodermia tylodes palmaris progressiva (Dohi and Miyake) J p J Dermat & Urol 29 9 5-1010 1929 Zbl 34 159

occupational causes play a part The condition has rarely been seen in boys The *favorable* influence of puberty is noticeable in certain dermatoses This is true of urticaria pigmentosa and of infantile eczema Only a small percentage of cases of infantile eczema are carried over into adult age in the form known as atopic dermatitis Such a stubborn and resistant disease as tinea of the scalp particularly microsporia, has a marked tendency to heal spontaneously at puberty although there are exceptions to this rule The fact that tinea of the scalp usually heals at puberty may be due to the higher acidity during puberty The pH of the infantile skin drops from 6 2 — 6 4 to 4 5 — 5 6 [1531]

[1531] Bancroft J R Hormones and Skin California & West Med 61 60 62 1944

Chapter XXII

MENSTRUATION

The Menstrual Cycle[1162, 1339, 153]

The anterior pituitary by means of prolan A a protein like hormone activates the ovary The follicle stimulating fraction of the prepituitary hormone causes the maturing of the graafian follicle during the first half of the menstrual cycle the luteinizing fraction prolan B after the ovulation on the fourteenth day makes the corpus luteum grow in the empty follicle

During the entire cycle the follicle secretes the steroid estrogens The estrogen blood level reaches its peak immediately before the onset of the menses and drops to its lowest point during menstruation There is another peak at the time of ovulation at midterm The estrogens cause the proliferative changes in the uterine mucosa during the first two thirds of the cycle The corpus luteum produces another steroid hormone progesterone which reaches its high in the circulation during the last third of the intermenstruum It causes the premenstrual secretory changes of the uterine mucosa which are preparatory for the embedding of the ovum If there is no fertilized ovum forthcoming the uterine mucosa breaks up and menstruation results The corpus luteum wanes

More than fifty years ago when menstruation was still believed to be a reflex von Ott[1533] the first to speak of a menstrual cycle traced over a full month the pulse temperature blood pressure caloric loss muscular power capacity of the lungs and other physiological functions He found that all these manifestations of vitality increased slowly in intensity during the whole intermenstruum to reach a maximum immediately before the onset of the menstrual flow Then a steep decline during menstruation brings the levels back to the starting point Since these studies many investigations have been made along the same lines They mostly revealed parallel cyclic changes of vitality and reactivity Many of the cyclic phenomena can be linked with cutaneous changes

Blood —The number of erythrocytes decreases slightly during the intermenstrual period During menstruation it first rises then falls and rises again after menstruation (Polzl after Novak[1470]) The hemoglobin fluctuation is slight There is a moderate leukocytosis during the first day of menstruation

The *thrombocytes* reach a maximum at the time of ovulation and a minimum during menstruation Catel and Schotola[1534] traced the decrease of the thrombocytes to the influence of the corpus luteum hormone and suggested the use of the reaction of the thrombocytes as a test for the potency of corpus luteum

[153] Frank R T Puberty Menstruation Pregnancy Bull New York Acad Med 16 83 97 1940

[1533] Von Ott D Des lol de la périodicité d la fo ction physiologique dans l organisme féminin Arch d obst et de gynéc 5 502-506 1890

[1534] Catel W and Schotola H Thrombocyte Menstruation und Corpus-luteum Hormon Med Klin 36 973 976 1940

preparations The tourniquet test is often positive before[1535] and during menstruation [1536 1537 1539] *The prothrombin level is probably lowered and the coagulation time lengthened shortly before the onset of menstruation* With menstruation rise of the prothrombin and return of the coagulation time to normal or even higher than normal takes place

The *blood sugar* shows a premenstrual rise [1540] The carbohydrate tolerance is lowered in menstruating diabetic women and acidosis and coma may be precipitated The more frequent occurrence of acidosis in women below forty five years of age than in males of this age may be linked to the influence of the menstrual hyperglycemia [1541 1542]

High blood *cholesterol* has, in some cases been seen to return to normal during menstruation [1543] It seems that the blood cholesterol falls during or near menstruation and is followed by a rise above normal level [1544 1545]

There is a tendency to premenstrual *water retention* One third of forty two women showed weight increase before and during the catamenia In some cases edema is noticeable[1546 1548] especially about the lower legs and ankles The urticarial (lymphagogue) reaction to intracutaneous injections of minimal doses of morphine is stronger in the premenstrual period while the vasoconstrictive action of adrenalin is weaker at the same time [1549]

The general hydration is probably accompanied by increased succulence of the skin which explains the menstrually increased firmness of the hair implantation in the skin [1550] On the last premenstrual day it takes more than double the weight necessary to pull a hair out than at the end of the period

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[1535] Bickel L J ann da Endothelsymptom als Test für Diagnose und Therapie ovariell r Funktionsstöru gen ange ehen w rden? Deutsch med Wchnschr **57** 1105 1106 1931

[1536] Deglmann T Akute Entzündungskrankh iten und Prämenstruum München med Wchnschr **25** 31- 1940

[1537] Adams W D r Prothrombinspi g l im Zyclus der geschlechtsreifen Frau Zbl f Gynäk **66** 105 1061 194?

[1539] Steissling r F Proth ombin Level a d Coagulation Time of Sexually Mature Wom n Ztschr f l g exp r M d **113** 37 1 1913

Bu l l J Di Capillarresi tenz und ihre B zi hung n zur Menstruatio bei der Frau klin Wchi sch **20** 266- 68 1941

[1540] S mo H C and Her mann F Sugar Metaboli m and Insulin Therapy in Acn Vulgaris Brit J D rmat **51** 477 1939 **52** 1 3 128 1940

Cramer H J Th Influ nc of M n truation on Carbohydrate Tolerance Cana l M A J **47** 51 1942

[1542] Kahl r H Einflu s de Men ruation auf d n Blutzuckerg halt Wi n klin W h schr **27** 017 018 1914

hmi lt F Choleste in un l Xanthom D rmat Ztscht **21** 137 1914

Ok y R a d B y l n R F Stu ly of th M taboli m of Wom n Lipi l Cont nt of Blood an l Me st ual C y l J Biol Ch m **72** 261 1927

[1545] r ria D a l M rmorston J Natural Resistanc and Clinical Medicin Boston 1941 Litt Brown & C

[1546] Swee y J S M n trual E l ma Pr limi ary Repo t J A M A **103** 31 1934

[1547] Atki o A J and Ivy A C Me st ual Ed ma Controll l by Emm nin but not by Theelol or Thee li J A M A **106** 515 517 1936

[1548] Mol S and Crube I Mit d r Men truation usammenhäng n les Ded m unkla er Genese klin W h schr **13** 369 37 1934

[1549] Krol lk A and Lebe lev A S hwankung n d r R aktionsfä igkeit l r Haut bei Frau n in Al hängigk it v m arl l m n tru ll n Zyclu Sov t vest ven r l ? 31 1932 711 43 1?

[1550] Basler M n truation un l Haarwurz lfestigk it Med klin **35** 1111 1113 1939

In the intermenstruum the resistance against pull rises to a medium figure Newer investigations have in part failed to confirm these claims [1551]

Menstrual swelling of the *liver* was already observed by Chvostek [155] Menstrual icterus has been the subject of several investigations [1553]

Von Leszczynski[1554] found that in eighty seven out of one hundred menstruating women whom he tested with intracutaneous injections of 0 02 per cent trypan blue the disappearance of the deposit was faster than normal This test seems to demonstrate an increased activity of the *reticulo endothelial system*

The sensitivity of the skin to ultraviolet *light* in the premenstrual phase is often higher than normal The return to normal sensitivity to light occurs during menstruation beginning on the first day [1555, 1558] This may be correlated with the simultaneous fluctuations of the blood calcium potassium and iron[1555] and especially of the estrogens In this connection the observations of Hamilton[1559] concerning the significance of the sex hormones in the tanning of the skin of women may be mentioned In women who were either in the spontaneous menopause or castrated marked tanning occurred only after injection of estrone or testosterone propionate Then the pigmentation appeared in areas which as long as two months previously had been exposed to light while areas protected by the shoulder straps and the bathing suit did not tan Thus the steroid sex hormones acted like a photographic developer

Spontaneous *allergic reactions* like asthma [1560] as well as those elicited by tests are often stronger immediately before or during the catamenia The sites of old positive intradermal reactions may flare up again during menstruation [1561] Patch tests are sometimes negative when done in the intermenstruum and positive when repeated during menstruation (Tzanck and Sidi after Urbach[976]) Urbach[9 6] advises not to increase the dose for pollen desensitization during the menses because of the possibility of acute reactions The Dick test for scarlet fever is sometimes temporarily falsely positive during menstruation On the other hand a negative Dick test during menstruation is to be considered highly reliable Some observers[156] found the highest reactivity to various allergens on the last

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[1551] Whitaker W L Hair Root Strength and Menstrual Cycle J Invest Dermat 6 305 307 1945

[55] Chvostek Die menstruelle Leberhyperämie Wien klin Wchnschr 9 93 297 1909

[1553] Senato Menstruelle Gelbsucht Berl klin Wchnschr 9 615 618 1872

[54] Leszczyński R von Über den Einfluss der weiblichen Geschlechtsorgane auf das retikuloendotheliale System der Haut Dermat Wchnschr 101 1109 1117 1935

[1555] Guthmann H and Nagel W Ultraviolettlichtempfindlichkeit und menstrueller Cyclus Strahlentherapie 48 6 8 1933

[556] Dietel H Das Lichterythem und der Einfluss von Menstruationszyklus und Schwangerschaft Strahlentherapie 27 58 596 19 7

[557] Ellinger F Die Lichtempfindlichkeit der menschlichen Haut Ihre Bestimmung und Bedeutung für die Lichtbiologische Konstitutionsforschung Strahlentherapie 41 1 82 193

[558] Freund L Menstruelle Steigerungen der Strahlenempfindlichkeit der Haut Wien klin Wchnschr 48 182 18 1933

[155] Hamilton J B Significance of Sex Hormones in Tanning of the Skin of Women Proc Soc Exper Biol & Med 40 50 503 1939

[560] Blum R Asthmaprobleme Med Klin 30 568-571 1934

[561] Ga O Ueber unspezifische Reaction n der menschlichen Haut Dermat Wchnschr 72 841 855 19 1

[1562] Hansen Pruss O C and Raymond R Skin Reactivity During Menstrual Cycle J Clin Endocrinol 2 161 16 191

day of menstruation the next strongest in the midperiod and the lowest on the premenstrual day. Thus the greatest reactivity of the skin would coincide with the period of estrogenic deprivation. The sensitivity to tuberculin has been found greatly reduced during menstruation.[1563]

There seems to be little or no influence of menstruation on the results of serologic tests for syphilis.[1564]

Menotoxin.—Popular belief has always held that a menstruating woman exerts a poisonous influence on her environment. Dough kneaded by a menstruating woman would fail to rise and fruit canned in this condition would not keep. In 1878 the British Medical Journal discussed the question whether the

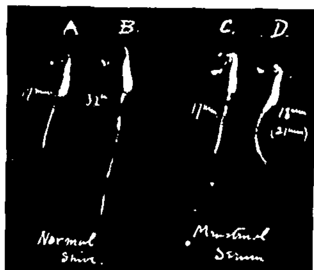


Fig. 201.—Toxic influence of menstrual serum on the growth of seedlings of lupinus albus. A and C, length of roots at the start. B, root after 24 hours in Shive's solution. D, after 24 hours in 1 per cent menstrual serum in Shive's solution. The root has increased only 4 mm. instead of 15 mm. Normal serum inhibits the growth also but much less. (From Macht, D. I.: J. Pharmacol. & Exper. Therap.)

general belief was true that if a woman cured hams while menstruating the hams would spoil. Similar beliefs are found in almost all countries.[1478] The question whether cut flowers wither quicker if handled by a menstruating woman was first studied seriously by Schick,[1565] who from his experiments believed that *the blood and sweat of menstruating women exert a poisonous influence on cut flowers and yeast.* He found a marked difference in the life time of cut flowers held over varying periods of time in the bare hands of menstruating women compared with that of flowers handled by the same person wearing rubber gloves or *in the intermenstrual period.* Dough kneaded by a menstruating person rose to only half the volume of the control.

[1563] Petersen, W. F., and Milles, G.: Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels, Arch. Int. Med. 38: 730-735, 1926.

[1564] Ingraham, N. R., and Mayer, V. R.: Menstrual Cycle and the Blood Serologic Test for Syphilis, Am. J. Syph., Gonor. & Ven. Dis. 24: 23-28, 1940.

[1565] Schick, B.: Das Menstruationsgift, Wien. klin. Wchnschr. 33: 395, 1920.

On the suggestion of von Gröer Schick[1565] called the hypothetic poison men otoxin Saenger[1566] in insufficiently reported experiments was unable to confirm Schick s[1565] claim of a menotoxin He experimented mainly with mice which after the injection of menstrual blood failed to show toxic symptoms The most interesting part of Schick s[1565] experiments which were in accordance with the popular belief was the toxicity of menstrual blood and sweat to plants Macht[1567] who had developed a much more sensitive and quantitative phyto pharmacological test method confirmed the existence of a menotoxin with well planned and controlled experiments He together with Lubin[1567] used the length of roots and stems of growing lupinus seedlings and the cultural growth of yeast as indicators They found a toxic substance present in the erum blood cells saliva sweat and milk of practically every menstruating woman With their seedling method it was possible to differentiate between the saliva of men struating and not menstruating women The hypothesis of a menotoxin (also toxic to small mammals) was later supported by several investigators[1 68 157] but the exact chemical nature of the menotoxin or the menotoxins is not known

As far back as 1923 Patzschke and Sieburg[15 3 15 4] had found that the choline content of the sweat of menstruating women was eighty to one hundred times higher than normal while at the same time in the blood the choline content increased only eight to nine times These findings substantially confirmed by Klaus[1575] suggest an elective accumulation and excretion of the metabolic toxin in the sweat glands[15 6] or its production in the skin The high choline concentration in the sweat or in the skin may well be one of the causes of men strual exanthemas[1573 1577] Macht in more recent studies[1571] suggests that the phenanthrene derivatives cholesterol and oxycholesterol might be menotoxins The substances are related to the steroid sex hormones One also has to consider certain highly toxic substances in the menstrual discharge Such toxins are formed in the endometrium[15 0] The histamine content of the menstrual blood is much higher (12 5 to 2 000 times) than that of the circulating blood[15 8] In creased activity of the apocrine sweat glands during menstruation is likely The gonadal relationship of these glands is known (See Puberty Menopause)

The hairdressers claim that permanent waves are not successfully given during the menses but this has not been proved

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[1566] Sa ng r H Gi t es ein Men tru tionsgift? Zbl f Gynäk 45 819 19 1

[1567] Ma ht D I an l Lubin D S Phytopharmacological Study of M nstrual To in J Pharm. & Expe Th rap 22 413-466 19 4

[1568] M mmsen a d Fitz M nst uationsgift Mo atschr f Ki d rh. 51 394 1932

[1569] Momms n H M n truatio sgift Mün hen med Wchnschr 81 1458 1934

[1570] mith O W and Smith G V Stu lies on M nstrual Discharg Proc Soc Exper Biol & Med 55 85- 7 1944

[1571] Ma ht D I Studies on M nstrual Toxin Am J M Sc 206 81-305 1943

[1572] Colom r L A El mito ginecologico l las m notoxi as Medi ina Española 11 30?-31 1944

[1573] Patzschk W and Si b rg F Zu A tiologi der M nstrual a th me Arch f Dermat u yph 146 55-62 19 3

[1574] i burg F and Patzschk W M nstruation un l Cholin toff echsel Ztschr f xpe Med. 36 324 19 3

[1575] Klau K Zu Frag les M no oxins Bioch m Ztschr 163 41 19 5

[1576] Rothman St a l haaf Fr Ch mi d Haut Ha db d H u Ck 1 2 161-3 ? 1929

[1577] Ottenst in B an l Böhm A Acetyl holin und histaminartig Stoffe im Hautdialysat Klin Wchnsch 14 275-276 1935

[1578] Gilberti I G an l Vand lli J M n trual Blood Contains Histamine in Notabl Quantities Boll Soc ital bi l per 17 234 194

day of menstruation the next strongest in the midperiod and the lowest on the premenstrual day Thus the greatest reactivity of the skin would coincide with the period of estrogenic deprivation The sensitivity to tuberculin has been found greatly reduced during menstruation [1563]

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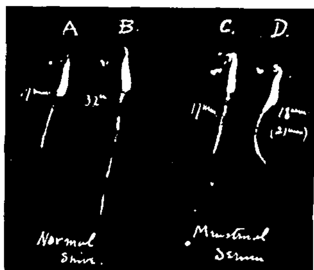


Fig 201 —Toxic influence of menstrual serum on the growth of seedlings of lupinus albus A and C length of roots at the start B root after 24 hours in Shive's solution D after 24 hours in 1 per cent menstrual serum in Shive's solution The root has increased only 4 mm instead of 15 mm Normal serum inhibits the growth also but much less (From Macht D J J Pharmacol & Exper Therap)

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[1563] Petersen W F and Milles G Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels Arch Int Med 38 730-735 1936

[1564] Ingraham N R and Mayer V R Menstrual Cycle and the Blood Serologic Test for Syphilis Am J Syph Gonor & Ven Dis 24 23 28 1940

[1565] Schick B Das Menstruationgift Wien klin Wchnschr 33 395 1920

the menstrual cycle Successful endocrine therapy is an important argument for the hormonal origin of menstrual dermatoses The increased knowledge of allergy has done much to explain the menstrual repetitions of some skin lesions As early as 1907 Wolff Eisner[1581] suggested the allergic nature of *menstrual urticaria* The regularly repeated fluctuations of a great number of substances which may have allergenic qualities and the increased reactivity provide an excellent set up for allergic phenomena It is to the merit of Geber[158] to have been the first to demonstrate the allergic character of some menstrual dermatoses In a case of menstrual urticaria he took serum during the time of menstruation and injected it intravenously into the patient during the intermenstruum This injection was followed by an outbreak of urticaria while it was not possible to elicit such a reaction with serum taken during the intermenstruum Menstrual serum from another woman did not work in the patient and the menstrual serum of the patient did not work in another woman The passive transfer with the method of Prausnitz and Kuestner was accomplished and desensitization by means of systematic injections of the autogenous menstrual allergen during the intermenstruum was found to be effective in a considerable number of cases

Waldbott saw premenstrual urticaria asthma and sneezing after a severe allergic shock caused by an injection of theelin This observation is of great theoretical interest but so far the evidence is scant [1582] Successful desensitization with ultrafiltrate of menstrual blood has also been reported Menstrual angioneurotic edema is not rare

The menstrual dermatoses have a definite tendency to recur in the same place as a fixed eruption This suggests that unknown factors of the terrain play a part in the pathogenesis It is sometimes possible to change by local X ray treatment the reaction of such an area and to prevent the recurrence Since many women take antipyrine for the relief of menstrual symptoms and since antipyrine is known to cause fixed drug eruptions this possibility has to be considered It sometimes needs the increased sensitivity of the premenstrual period to produce an antipyrine eruption [1584] It is of historical interest that the first fixed antipyrine eruption which was described by Brocq in 1904 occurred in a patient who took antipyrine for painful menstruation The eruption was at first ascribed to her periods (Abramowitz in discussion to Throne[1585])

In *menstrual urticaria* the eruptions are sometimes confined to the vulva and the surrounding areas In the typical cases the picture is the same as in nonmenstrual cases of hives

Angioneurotic edema mostly of the lips or eyelids also occurs in connection with menstruation In one of the author s cases the first attack occurred after

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[1581] Wolff Eisner Über die Urticaria vom Standpunkt der neuen Erfahrungen über Empfindlichkeit gegen körperfremde Eiweissubstanzen Dermat Zbl 10 164 177 1907

[158] Geber H Einige Daten zur Pathologie der Urticaria menstruationalis Dermat Ztschr 32 143 150 1921

[1582] Waldbott G L In Discussion to C I p I H Allergy to Pancreatic Tissue Extract J Allergy 12 1 5 1941

[1584] Szary A Bureau Y and Horowitz A Dermatoses cataméniales médicamenteuses Bull Soc franç de derm et syph 44 805 809 1937

[1585] Throne B Exanthema menstrual angioneuroticum Arch Dermat & Syph 21 10 5 1930

a childbirth and recurred menstrually for twelve years This type of onset after pregnancy has also been observed in other cases [1586]

Menstrual dermographism is known

Pruritus vulvae menstrualis is not very rare It is usually taken as a part of the natural congestion of the vulva during the menses and treatment is seldom requested

Infections

The menstrual period is accompanied by a lowered resistance to many infections [1584 1587 1588] Many surgeons avoid operations during menstruation because of the increased tendency to inflammatory complications The self disinfecting power of the skin surface is reduced as shown by Fisher[1589] in systematic investigations with *Bacillus prodigiosus* The serum of menstruating women shows little or no disinfecting power during the last ten premenstrual days in vitro tests with anthrax bacilli (Drexel and Keller quoted by Geller[1590]) Scarlet fever diphtheria tonsillitis and furuncles often start during menstruation It is known in hospitals that girls admitted because of scarlet fever and diphtheria are usually menstruating [1591] This general experience was confirmed by a study of hospital nurses They too were often menstruating when they came down with scarlet fever [1592] Of 119 women in the menarche almost 50 per cent were menstruating when they entered the hospital having erysipelas The menstrual character of the infection is more obvious if the outbreak coincides with menstruation more than once Menstrually recurrent erysipelas is often dealt with in the older literature [1483] Cases with 50 recurrences of erysipelas have become known Erysipelas at the time of the expected but absent menses in one case eight times in succession has been recorded Jerusalem s[1593] observation of eight cases of monthly recurrent erysipelas in males has not been repeated The whole matter of menstrual erysipelas has during the last twenty five years[1594] found little interest Premenstrually recurring paronychia has lately been described [1595] The author saw a case of hidradenitis axillaris which over years recurred quite regularly with the menstruation In another case a furuncle like deep ulceration of the perineum which took two weeks to heal accompanied many periods

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[1586] Ballerini Quincke s Disease and Pregnancy S) Emilina e Marchigiana di t gin 28 1 1313 Abstr D rmat W hnschr p 1218 1913

[1587] Sprunt D H The Part Played by Age and the Female Sex Hormones in Resistance to Infection Endocrinol 25 6 6-8 1933

[1588] Sprunt D H McDearman S and Raper J Sex Hormones and Infection J Exper Med 67 1 9 168 1938

[1589] Fisher S Variations in Self Disinfecting Power of the Skin During the Menstrual Cycle Proc Soc Exper Biol & Med 28 9 353 1931

[1590] Geller F C Infektion und menstrueller Zyklus München med Wchnschr 87 1110 1940

[1591] Mayer F C Empfänglichkeit gegen Infektionskrankheiten und Menstruationszyklus München med Wchnschr 87 91 1940

[1592] Horstmann H Eckhardt F and Northausen W Empfänglichkeit gegen Scharlachinfektion und Menstruationszyklus München med Wchnschr 87 40 -403 1940

[1593] Jerusalem B Beziehungen zwischen Menstruation und Erysipel Wien klin Rundschau 190

[1594] Blumlova N O mestli Erysipeloides Menstrualis ... Dermat 6 47 10 1929 711 31 74

[1595] R H J C Paronychie als h vor der Menses wiederkehrendes ... Münch med Wchnschr 88 ... 1941

Menstrual *herpes* the infectious nature of which has been established [1596] is the most common menstrual dermatosis About three out of four cases of genital herpes in the female are due to menstruation (Bergh after Steuer[1453]) In its appearance menstrual herpes is no different from herpes simplex After a premonitory burning sensation of a few hours red spots appear which quickly develop into crystalline vesicles These blisters form one or several small groups They become pustular after one or two days then they dry up and heal without scars in about one week The primary blister is quickly destroyed on mucosal surfaces Here the typical appearance is a whitish or red spot with floating remnants of the blister at the edge On the skin as well as on the mucosa the blisters may merge to form plaques The local lymphatic nodes are often tender and slightly enlarged Next to the genitals the lips and the chin seem to be the most common sites of the eruption Just as the menstrual acne the menstrual herpes is often seen on the chin Fournier[15] aptly called this herpes indiscret Eruptions on the hands on the thighs or elsewhere are much rarer Unusual and more serious events are menstrual herpes eruptions of the cornea[1597] and of the oral and pharyngeal mucosae The latter sometimes known as herpetic angina can be accompanied by rather severe constitutional reactions [1598] The experimental transmission of menstrual herpes into the rabbit cornea has not only been successfully performed [1599] but contact infections in man are known [1600] Menstrual herpes appears most often immediately before menstruation but in some instances during or after menstruation The first attacks have been seen to precede the menarche several times in monthly intervals [1601] It may occur at characteristic intervals in pregnancy [160] or if actual menstruation is disturbed by disease malformation or aplasia of the internal genitals [1603] It may also continue to appear for a short while in the early menopause

Menstrual *acne* is usually a menstrual flare up of chronic acne lesions Possibly in connection with an increased premenstrual activity of the sebaceous glands After the catamenia the acne lesions become dormant again Macht[1571] found the menstrual sera of women suffering from acne generally more toxic to seedlings than such sera from women who did not have acne The blood of young men with acne rarely exerted a phytotoxic reaction The exacerbation of acne appears in some patients before in others during or after the menstruation often keeping this time relationship remarkably constant [1508] Some authors claim that the chin is frequently affected by menstrual acne

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[1596] Lipschütz B W it re Untersu hung n über di Aetiologie des Zo t r I Ueber die Mikroskopi der Impfres tio und des g n rali ie t n Bläsch exanthem na h Impfung mit Zoster A h f Derm t u Syph 149 196- 06 19 5

[1597] Med n y r A M nstru lle H rpesre idive Zbl f Gynäk 49 2691 2695 19 5

[1598] Lava F Recurri g Herpetic Angina Oto- hino-lary g Int rnat 24 ? 3 1940

[1599] Keining R zidi i nd H rpes impl x m nstruali am 3 u d 4 Fing r d r link n Hand mit ry ipelatöser Anschw llung des Handrü k n un l d Aussenseite des Unt ra m Zbl 43 ~ 4

[1600] Tou l A R nault I and ouligna Herpes récidivant tra nis par un port ur al de viru Bull Soc Fra ç d d rmat t yph 41 645 193

[1601] B ttman 9 H rpes s xuali D utsches Arch f klin. Med 88 153 1907

[1602] Pi semann M nstru tl n h pes A ta d m t vene eol 1970 al tr D rm t Wchnschr 71 8 3 1970

[1603] Sol mo s B H pes as a Type of Vicarious Men truatio Dublin J M Sc 4 217 19 19 1

Hemorrhagic Dermadromes —The hemorrhagic tendency is increased during menstruation and the platelet count is lowered Menstrual *purpura* of all degrees of severity has been known for a long time The purpuric lesions may be petechiae or larger hemorrhagic spots They may be universal or restricted to certain areas e g the lower half of the body[1604] In purpura as in other menstrual rashes there exists a tendency to fixed recurrence Such fixed purpuric lesions have been seen to recur regularly e g around the eyes[1605] or on the thighs[1606 1607] Menstrual purpuric exacerbation is sometimes observed in conditions which themselves have a hemorrhagic tendency Menstruation then provides an additional hemorrhagic factor Cases which allow such an interpretation include one of menstrual purpura in a girl with mitral stenosis[1455] and cases of rheumatic fever[1458] Here also belongs the case of a petechial menstrual crop on the lower legs which appeared only while a tapeworm was present in the bowel After removal of the tapeworm the rash failed to appear but recurred menstrually after the recurrence of the taenia This happened four times[1608] The bleeding may occur in any open lesion

Varicose luetic or other ulcers have often been observed to bleed during menstruation This phenomenon about which much has been written in the last century has hardly found attention within the last generation Another type of *menstrual ulcer* improves or heals during the intermenstruum and recurs during menstruation More often than the menstrual ulcer has the related *vicarious or ectopic menstruation* been studied In most of the instances the term was used incorrectly since vicarious menstruation should be called only a discharge of blood from some organ other than the uterus with suppression of the menses (Webster) This type has been called substitutional menstrual hemorrhage while for extragenital bleeding of any form occurring together with the bleeding from the uterus the term additional or complementary menstruation should be applied[1478] This mysterious phenomenon has a history in which early over estimation was followed by complete denial of its existence during the late nineteenth century But since then so many observations have been recorded that a reserved but positive attitude has become general It is well illustrated by a statement credited to Lawson Tait who said that he does not deny that there is such a thing as vicarious menstruation but he does deny the propriety of examiners *asking the commonest cause of epistaxis and receiving the answer of* vicarious menstruation with approval[1609]

The nasal mucosa is the most frequent source of vicarious bleeding This *is not surprising since menstrual swelling of certain areas of the mucosa covering*

[1604] John Purpura dysmenorrhoica Zbl 45 291 1933

[1605] Beerman H A Case for Diagnosis (Cutaneous Vicarious Menstruation? Hysteria) Arch Dermat & Syph 33 759-760 1936

[1606] Hirschberg A Ueber die Beziehungen der Menstruation zur Haut Ztlf f Gynäk 48 1966-1967 1924

[1607] Halter Prämenstruell rezidivierendes fixes Ekzem nach Salvarsan Dermat tl Ztlf 58 413 1938

[1608] Winkler F Menstruelle Ekchymosen durch Darmparasiten hervorgerufen Dermat Wchnschr 64 469 1917

[1609] Condit W H Compensatory (Vicarious Ectopic) Menstruation X nom la Memm a D 0 Am J Obst 73 238 251 1916

the lower turbinates and the tuberculum was long ago observed by Fliess[1610] who found these areas during menstruation invariably swollen hypersensitive and apt to bleed on the slightest touch

While ectopic menstrual bleeding from the gastrointestinal canal the lungs and the mammary glands have been observed relatively often sometimes under alarming circumstances the skin seems to be a rare source Condit[1609] saw a hematoma of hen s egg size develop from a small nevus on the chest in menstrual intervals after the uterus and the adnexa had been removed After excision of the nevus hemorrhage in the breast occurred Other reported sources of vicarious menstruation include old scars endometriomyoma of the umbilicus[1611] the nailbeds the lips and gums Bleeding from fistulae cancerous lesions and hemorrhoids must be interpreted in the same way as the menstrual ulcer[14 3 14 8]

The menstrual history of these cases often reveals irregularities Puberty and still more the approaching or beginning menopause seem to predispose Several cases have been observed after hysterectomy[14 8] Since extravasations are mong the manifestations of hysteria it is not surprising that psychopathic individuals are often found among the afflicted For the sake of curiosity a twenty four year old male sexual psychopath with unusual psychic attachment to his mother may be mentioned[1612] He developed monthly cutaneous extravasations in his right arm pit

Erythemas

Besides such clinically well characterized menstrual dermatoses as herpes urticaria and purpura a great variety of transitory menstrual erythemas have been observed The simplest form is the noninflammatory erythema of the face which sometimes marks approaching menstruation It seems to be a first step towards rosacea which has a marked gonadal relationship (see Rosacea) Occasionally the congestion may involve the conjunctiva[14 1] In some cases roacea starts as a menstrual erythema in the blush area and becomes a stable erythema during the menopause Some menstrual erythemas have the characteristics of erythema exudativum multiforme with nummular papulo-erythematous lesions on the face neck forearms and lower legs Some are more vesicular and some show a small vesicle in the center of the red lesion Typical are the herpes iris forms while gyrate or erythema nodosum like lesions are not extremely rare[1451]

There is a tendency to fixed eruption More rarely the appearance is vicarious appearing only at the time of the missed menstruation Some of the cases which have been described as menstrual erysipelas probably belong to the erythemas In some cases tonsillectomy[1613] or staphylococcic vaccine cured menstrual crops of erysipelas resembling erythemas

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[14] Fliess Bezi hung n zwisch n Nase und weibli h n Geschlechtsorganen Leipzig 1897

[1] F z r N Endometriomyoma of the Umbilicus Arch Path 10 879 856 1930

[1] Hadley E L Axill y Men truation in a Male Am J Psy hiat 9 1101 1111 1930 Zbl 36 14 1931

[14] I m rl D Fälle von Toxicoderma m ustruale mit erysipeloidartigen Erscheinungen Magy Nögyógy 8 199- 01 1936 Zbl 56 614

Fig 20 —Menstrual eruption re embli g ryth ma multif rme



Fig 206 Fixed m trual ruption of ec m tou haract r receil g alm st ntirely d i ing th li t rm n truum

Miscellaneous —Menstrual *chromidrosis* of which substantiated reports can be found in the older literature[1453] has not been heard of during the last fifty years It seems that the discolorations of the sweat either were feigned or caused by staining substances from without and not by excreted indigo as had been suggested *Bloody sweat* has several times been seen in menstrual attacks It is a hemorrhagic phenomenon of the same significance as other purpuric symptoms

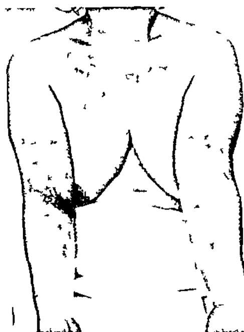


Fig 07

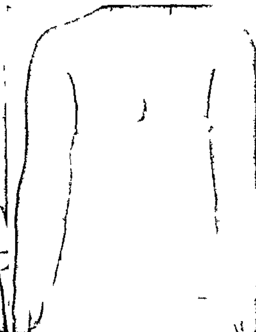


Fig 08

Fig 907 —M nstrual d natit (From Urbach E Allergy Grune & Stratton Inc)
Fig 08 —Same patie t in I te m truum (From U ba h E Allergy Grune & Stratton Inc)

The menstrual darkening of freckles of the linea alba or of other *pigmentations* is occasionally quite marked The greater pallor of some menstruating *women or a rudimentary chromatophoric function of the anterior pituitary* may be suggested as an explanation No recent investigations have been publi hed Ruhl s[14] observation of menstrual discoloration from gold jewelry has not found much confirmation Naturally one has to think of silver sulfides developed in more vi ible amounts by increa ed menstrual sebaceous secretion Menstrual soreness of the mouth and aphthous ulcerations may become quite troublesome In ome cases these eruptions can be prevented by theelin [1614]

[14]Heidemann M and Andersen B G Oral Manifestations of Ce tain Systemic Disorders Yal J Biol & Med 17 583 594 1945

Treatment—In all menstrual eruptions correction of any hormonal disorder should be tried Sometimes the eruption fails to recur if normal menstruation can be restored But this is not always true In some cases menstruation is normal except for the rash but the rash may yet be cured by theelin [1614] Not only theelin but theelin in the first half of the intermenstruum and progesterone in the second half has been given successfully (Urbach[976]) Other hormones or combinations of hormones e g a placenta preparation and dried adrenal glands[1615] have occasionally helped

A method of treatment which should be tried in all refractory menstrual eruptions is Geber s desensitization to premenstrual blood[1616] which has been successful in a considerable number of cases Urbach[976] describes the technique as follows About 20 c c of blood is taken at the acme of the premenstrual exacerbation There is some difficulty in determining the right time since much seems to depend on getting the most potent allergen The blood is centrifuged and the serum poured into a rubber capped bottle After 1 10 000 of merthiolate has been added the serum is stored under refrigeration Then 0 2 c c of serum is injected intracutaneously every second day The injections are given four successive times into the same site The site of injection is changed after eight to ten days Lehner and Rajka (after Urbach[976]) inject 0 4 c c daily into two areas in corresponding symmetrical sites While this method was originally used in menstrual urticaria it later proved to be effective in other menstrual dermatoses and complications also e g in menstrual trigeminal neuralgia [1616]

[1615] Adrenal Substance in Dermatoses Which May Have a Menstrual Factor Arch Dermat & Syph **31** 865 1935

[1616] Géber H Desensibilisationsversuche bei Menstruationsintoxikationen Med Klin **31** 1 03 1?04 1935

Chapter XXIII

PREGNANCY

The fertilized ovum after its implantation into the uterine mucosa causes profound changes in the hormonal balance Within a few days after the first missed period the anterior pituitary like hormone (chorionic gonadotropin) from the placenta increases in the blood as well as in the urine and reaches a level many times higher than normal after about sixty to ninety days This peak subsides and remains at a lower but still elevated level until delivery The estrogen content of the blood and urine increases progressively from the second month until near term The progesterone level rises until after the fifth month when the corpus luteum undergoes involution The ratio of the estrogens changes and may assume an abnormal pattern in pre eclampsia [1519] With the expulsion of the fetus and placenta a rapid return to the pregravid state ensues with a slump in the normal production of hormones [153 1617]

It is natural that the hormonal upheaval of pregnancy is associated with profound changes in the entire endocrine system

The anterior lobe of the *pituitary* increases to two and one half times its usual weight and there are characteristic microscopic changes The large amount of pituitary gonadotropic hormone in the blood and urine is well explained by this hypertrophy This may account for various stimulations of growth of the skin and its appendages

After the third month the *thyroid* gland increases in size in almost all cases and its activity is stepped up Iodine moves from the thyroid into the blood reducing the glandular iodine level about one half The basal metabolic rate is often raised If the thyroid is unable to meet the increased demand for thyroxin hypothyroidism may develop The hyperthyroidism of pregnancy may explain certain sensations of heat hyperhidrosis and erythema

The *parathyroid* glands too are stimulated probably due to the high demand for calcium for the child s skeleton The calcium deposits in the mother are drained The blood calcium level is lowered Inability to meet the increased requirement may cause a state of hypoparathyroidism with tetany The ovaries swell and the follicles continue to develop but fail to ripen The *corpus luteum verum* provides an uninterrupted supply of progesterone needed for implantation the prevention of uterine contraction and the formation of the decidua After the first half of the pregnancy the corpus luteum undergoes involution to prepare the termination of pregnancy Some of its functions are taken over by the pituitary and the placenta The increased secretion of estrin changes the microscopic picture of the vaginal smears The epithelial cells increase in size during the first months Later they become smaller again so called oyster shaped cells appear and leukocytes abound Just before labor the desquamation of the

[15] Freed S C Glandular Physiology and Therapy Chicago 1941 American Medical Association

vaginal mucosa almost reaches denudation The *adrenal* cortex hypertrophies during pregnancy to meet the greater demand That the demand is greater has been shown by the fact that adrenalectomized cats need more cortical extract for *survival during pregnancy than when nonpregnant* The lowered glucose tolerance of pregnancy is perhaps caused by a *hyperactivity* of the adrenal medulla though it has been ascribed to pituitary pancreatic liver and renal factors In the *liver* glycogen disappears from the central portion of the lobules and bile stagnates in the biliary channels

During the latter part of pregnancy a great amount of nitrogen is stored in the maternal system beyond the need of the fetus The blood N P N falls *Albuminuria is common*

The fat content of the blood increases after the third month giving the blood serum a cloudy appearance The *alkalinity of the blood is increased* Cholesterol is increased in the blood and in the adrenal glands The blood cholesterol (not the cholesterol esters) increases about 100 per cent[1818] There is a retention of sodium potassium magnesium and sulfur and the excretion of iron and phosphorus is decreased The retention of most of the minerals exceeds the needs of the growing fetus

Normal Skin Changes —The skin responds to pregnancy in many ways According to the majority of the observers the *perspiration* is increased especially towards the end of the pregnancy Extreme degrees of hyperhidrosis have been seen[1819] in this period *The increase of sweat secretion may take some strain off the kidneys The urea may rise in the sweat with increasing renal insufficiency* Chlorine increases in the sweat during the first half of the gestation but decreases later In toxemia *it* is greatly reduced[1820] Prolan appears in the sweat of the pregnant women[1821]

An actual hypertrophy of the sweat glands which had been claimed earlier[1822, 1823] does not seem to have been confirmed in more recent investigations *It has been suggested that the growth of the sweat glands in pregnancy is part of the acromegalic tendencies* caused by *the pituitary changes*[1824] The *perspiratio insensibilis* decreases with the progress of the gestation but increases during the puerperium The loss of water through the skin is particularly low in toxemia[1821, 1825]

The apocrine glands the gonadal relationship of which has been mentioned in the chapter on Puberty probably cease to secrete during pregnancy[1176] The secretion of the *sebaceous* glands increases during the latter half of gestation

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[1818] Schaaf F Der Lipoidstoff wechsel Z … 23 1-32 193 212 1930

[1819] Pohl B Hyperidrosis gravidarum Zbl f Gynäk 50 2767 2769 19 6

[1820] Glu … The skin organs (?) excretion in the Toxemias of Pregnancy … glace 37 3…-350 1931

[1821] Conseil … Le prolan … 26 … 1931

[1822] R… … Schweissdrüsenapparat in der Schwangerschaft … 1911

[1823] … Ueber die Beziehung … Haut … der endocrinen Drüsen Z… 12 … 19 …

[1824] Puhr … Hautveränderungen bei der Menstruation und in der Gravidität in ihrem Zusammenhang mit der innersekretorischen Tätigkeit … Keimdrüsen Arch f Frauenk u Eugenik 7 77 79 19 …

[1825] Seitz L Die Schwangerschaftstoxikosen Gestosen und Dyskrasien In Halban & … Biologie und Pathologie des Weibes vol 7 Berlin 1927 Urban & Schwarzenberg p 792

This seborrhea is especially marked during the last five days[16 6] and during labor Soon after delivery both hyperhidrosis and seborrhea return to normal It is interesting that the seborrhea of pregnancy is only rarely accompanied by acne[1627] Usually existing acne is improved This suggests that not seborrhea but other factors (comedones) are the cause of juvenile acne

Implantation of particles of normal skin of pregnant women into rats and infantile mice produces the same changes as the pregnant woman s urine It does not elicit the Allan Doisy reaction This proves that prolan and not estrogen is the active principle The prolan is apparently stored in the skin Skin which has been rendered anemic is not less and skin with the pigmentation of pregnancy is not more effective than normal skin[1628]

The epidermal mitoses are more numerous in pregnancy at least in the guinea pig[16 9] This indicates a stimulated growth which manifests itself in an occasional thickening of the skin in hypertrichosis and in the development of small neoplasms The lips may appear thicker the features coarser and the facial expression may well resemble an early stage of acromegaly

Pigmentation —During pregnancy certain areas of the skin which already have a tendency to increased pigmentation receive a stimulus to produce more pigment than in the nonpregnant state Scars particularly those from abdominal operation often take part in the pigmentation Brunettes become much more heavily pigmented than blondes Generalized melanosis and darkening of larger but circumscribed areas adjoining the well known physiological sites of pigmentation although a little more common in pregnant hyperthyroid women[1630] is extremely rare The linea alba or more correctly the midline of the abdominal skin usually becomes pigmented in the third month of pregnancy but sometimes much later especially in blondes and multiparae[1453] This linea fusca or *linea nigra* as it is often called extends from the mons veneris to the navel and though less often and less pronounced into the epigastric region The line is about one third of an inch wide and varies in color from light greyish brown to deep brown or black If it extends to the epigastric area it often forms a one half to one inch wide brown ring around the navel which is called the umbilical areola of Montgomery The black line is present in 94 per cent of pregnant women It is occasionally missed in obese women and in very light individuals rarely in the darker pigmented women The pull of the ligamentum teres of the liver sometimes causes a deviation to the right of the supraumbilical part thus producing a bayonet shaped line

The areolae of the mammillae darken more intensely than the linea nigra the degree varying again with the color of the hair There is a certain amount of darkening around the areola proper This secondary areola consists of a network of brownish lines surrounding the lighter follicles The secondary areola

[626]Flo is M La s c ion s lacea i gravi la za Arch di sc Biol 17 71 86 193
[16] S itz L S hwang rschaft to ikos n und Ha t Zbl 27 3 19 8
[1 7]Loeser A Die Haut als H rmo träg r in d r S hwang rschaft Zbl f Gynäk 56 1155 193
[ ] Loeb L and Haven F L Th R lation B tween States f th S x Organs in the F male *Guin a-pig a d th C ll Proliferation f the Epidermis* Anat Rec 43 1 6 19 9
[ ] Fulenn G La pigm ntation à type addisoni n dans la maladie de Based w Rev f anç d endocrinol 6 193-206 19 8

though being a sure symptom of pregnancy does not appear before the fifth month [1631]

The hyperpigmentation of the vulva can reach extreme degrees The edges of the labia minora are intensely pigmented The discoloration may



Fig 209 Melanosis of pregnancy Note deviation of pigmented linea alba to the right caused by pull of ligamentum teres hepatis (Courtesy Division of Dermatology Department of Medicine University of Chicago)

extend beyond the vulva to the perineum to the inner aspects of the thighs and around the anus Rarely old scars and striae become pigmented The sensitivity to light increases in pregnancy which causes more ready tanning [1557]

The number of noticeable pigmented spots increases in about 25 per cent of the pregnant women Freckles or lentigo like spots appear or become more pronounced [1632, 1633] An unpigmented mole may become pigmented

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[1631] Kehrer E In Halban J and Seitz L Biologie und Pathologie des Weibes vol 6 Berlin 1926 Urban & Schwarzenberg pp 758 59

[1632] Jordan A Chloasma faciale bei jungen Mädchen nichtschwangeren Frauen und Männern Dermat Wchnschr 96 336-340 1933

[1633] Goldsmith W N Pigmentation Brit J Phys Med 11 43-46 1936

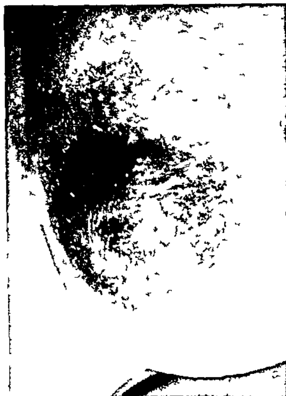


Fig 210 —Pigmentation of br ast in pregnancy



Fig 211 —Chloa ma persisting aft r pregnancy Irregular m nstruation

'Quae utero gerunt in facie maculam habent' Those who are pregnant have spots on the face This was known as a fact to Hippocrates but in the nineteenth century[1633] the connection of *chloasma* with the uterus was still the subject of much controversy It was either claimed that it had nothing to do with the uterus or that it was identical with tinea versicolor Chloasma is present in 74 per cent of all pregnant women in the later part of the gestation Only one third of the cases are marked, the rest are more often pale than pronounced depending much on the color of the skin and hair (F A Kehrer and Karl Hoffner after E Kehrer[1631]) The color may be deepened by exposure to light[1634]

The chloasma of pregnancy consists of sharply outlined often jagged yellow brown or grayish spots They are symmetrical and follow certain patterns[1635] They either appear as scattered small spots on the cheeks and nose or as a mask like discoloration which leaves the lids the surroundings of the eyes the pre auricular areas parts around the mouth the temples and almost always a narrow strip along the frontal hairline free In another type the temples and the zygomatic areas are dark while a trapezoid area in the center of the forehead remains light[1635] Transitional types between these patterns occur

Chloasma usually disappears within a short time after delivery The first menstruation seems to stimulate the bleaching Not infrequently the spots fail to vanish for a long time even for many years Chloasma has even been seen to persist in the menopause (Muratori after Sézary and Duruy[1636])

Chloasma like pigmentations are not exclusively seen in pregnancy They have been observed in young girls nonpregnant women and in men Chloasma periorale virginum is a type of stubborn chloasmatic pigmentation in the lips of young girls[557,1637] The nonpigmented narrow strip separating the chloasma from the vermilion border which originally was described as characteristic in this condition can be seen in many perioral pigmentations e g in perioral vitiligo

The pigment of pregnancy is melanin As such it is iron free[1638] and in its histological characteristics is no different from melanin deposits in other conditions

The cause of the pigmentations of pregnancy is seen by some authors in the adrenal cortical hypertrophy[1639,1640] There is no doubt about the existence of adrenal changes in pregnancy and about the connection of pigmentations with the adrenals but it has not been proved that just the pigmentations of pregnancy

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[1633] Mirowsky ? Schwangerschaftspigmentierung und Chloasma Handb d H u Gk 4 2 990 143

[1634] Schaly J Formen und Ursachen der sol Chloasma uterinum benannten Hyperpigmentationen des Gesichtes Dermat Ztschr 58 1 19 1930

[1636] Sézary A and Duruy A Chloasma Nouv ell pratique dermatologique vol 5 Paris 1936 Masson & Cie pp 9 5 9

[1637] Wyner ? h Chloasma periorale virginum (Foor) Zbl 22 17 19 6

[1638] Tscham ? ? Histological and Histochemical Study of Pigment in Pregnancy Arch f Gynäk 109 3 -310 193?

[1639] Grossmann H and Schi berg Ursach und Bedeutung der Schwangerschaftspigmentation Ztschr f Geburtsh u Gynäk 92 731 748 19 8

[1640] ?litsky ? Les dermatoses les toxidermies et les mélanodermies de la grossesse Gynéc et Obst 21 4 7 1930

are caused by the adrenal influence It has been shown[1644, 1641, 1645] that in animals as well as in man pigmentations identical to those in pregnancy can be produced by the implantation of ovaries or by the injection of large amounts of estrogen under certain conditions In pregnancy there exists a tremendous increase of the estrogen level The work of Bloch has so far given the best explanation for the pigmentations of pregnancy The pregnancy of one of a pair of siamese twins provided a unique observation The nonpregnant twin developed chloasma as well as the pregnant one Both chloasmas were concordant (Hübner after Meirowsky[1634]) This proves a hormonal or humoral cause of the pigmentation and at the same time the existence of certain local possibly hereditary factors necessary for pigment formation A hereditary factor in chloasma uterinum without pregnancy is established[1579]

It has been suggested that the vitamin C deficiency in pregnancy may have something to do with chloasma Vitamin C is known to exert an inhibitory influence on melanin formation at least under experimental conditions (see Addison s Disease) However it has not been established that prophylactic administration of Vitamin C in pregnancy prevents or heals chloasma[1646, 1647]

Statistical and tintometric investigations in a large number of pregnant women[1648] seem to corroborate the belief that heavy pigmentation is associated with an undisturbed pregnancy It is statistically correlated with less vomiting vigorous labor and less danger of atonic hemorrhage and perineal lacerations On the other hand Grossmann and Schoneberg[1639] based on laboratory studies deny any metabolic differences between heavily pigmented and nonpigmented pregnant women and attach no diagnostic or prognostic value to this phenomenon

Hypertrichosis —Occasionally the hair growth of the face and some other areas increases considerably during pregnancy This was already known[1449, 1649, 1650] when Halban[1651] (1906) discovered that hypertrichosis is a physiological phenomenon of pregnancy It is ordinarily so slight that it passes unobserved The light down on the face[165] as well as on the arms legs and the abdomen becomes a little heavier and darker Along the linea nigra it may or may not lead to a

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[1644] Lipschütz A Ueb den Ort d r Pigm ntbildu g Virchows Arch f path Anat 276 676-680 1930

[1641] Bloch B and Guldberg C Di Ur ach der Schwa g rschaftshyp rpigm ntl rung Klin Wchnschr 12 734 35 1933

[1642] Bloch B Erzeugung d r Schwa g rschafts-Hyp rpigmentl rung (Chloasma Lin a alba) beim Mensch n durch Inj ktion des Ovarialhormons (Oestroglandol) Zbl 46 15 1933

[1643] Bloch B U be hormonal Beei flussung de Pigmentbildu g Zbl 44 519 1933

[1645] Forbes Th R S x Ho mones a d Hair Cha ges in Rats Endocrinology 30 465-468 194

[1646] Tesch er F Chloasma Gravidarum and Vitamin C Kli Wchnschr 13 II 1614 1934

Hruszek H Chloa ma gravi larum—Vitamin C Münch n med Wchnsch 84 1336 1337 1937

[1648] Nishizaki S Studies on Skin Pigm ntation During Pregnancy Jap J Obst & Gy ec 11 41 43 19 8 Zbl 31 6? Jap J Obst & Gynec 12 368-370 19 9 Zbl 34 ?93 Jap J Ob t & Gynec 12 374-377 377-380 1929 Zbl 35 ? 6

[1649] locum A Ca of Hirsuties Gestatio is N w York M Rec 1875

[1650] Hegar A Zur abnorm n B haaru g B itr z G burtsh u Gyna k 4 21 1901

[1651] Halban J Uebe ein bishe nicht beobacht tes Schwangerschaftssymptom (Hypertrichosis graviditatis) Wien klin Wch schr 19 1906 20 1907

[1652] Ced rcreutz A Hypertri hosi superciliarium et in fronte in graviditate aperien Acta de mat venereol 20 704 1939



Fig 212 —Hypertrichosis of pregnancy (From Stoddard F J Am J Obst & Gynec 1945)



Fig 213 Same patient as shown in Fig 212 4 months after delivery Hypertrichosis which was so marked in pregnancy has completely disappeared Eyebrows appear less heavy (From Stoddard F J Am J Obst & Gynec 1945)

pronounced male type of hair distribution[1653] Occasionally a marked hair growth appears just in the midline quite different from the male distribution Halban[1651] showed that two weeks after shaving the abdomen of a pregnant rabbit was covered with thick hair while hardly any growth could be noticed in the controls It took less than half the time to restore the full hair of a preg nant rabbit than was necessary in the nonpregnant Similar observations have been made in other domesticated animals However the increased growth stops before the parturition[1654] The hypertrichosis of pregnancy usually disappears shortly after delivery and sometimes at the time of the first menstruation but it may reappear in subsequent pregnancies It is suggestive to relate the hypertri chosis of pregnancy to the hypertrophy of the adrenal cortex * Pituitary and thyroid stimulation may play a part

A pregnancy test based on the sulfur content of the hair compared with that of nonpregnant women has been described by Kossiakoff[1655] It has not found enough confirmation

Alopecia areata has a tendency to disappear in pregnancy but may recur shortly after parturition[1650] In some cases alopecia areata began shortly after pregnancy A seemingly paradoxical and rare phenomenon is the disappearance of hypertrichosis of the upper lip during pregnancy and its recurrence after par turition[1656]

The daily growth of the *nails* during pregnancy has been found to be in creased from 0 13 to 0 16 mm[1657]

Striae, Including Those Not Related to Pregnancy —Striae are stripe shaped lesions which by their form and arrangement across distended skin im mediately show that mechanical tension is a factor in their pathogenesis Though by far most common in pregnancy they occur in other conditions in most of which the skin is or has been under mechanical strain caused by enlargement of the volume of tissue which it covers

Since the striae of pregnancy are the most common example of striation the whole phenomenon may be discussed in this chapter The striae of pregnancy are linear or somewhat wavy stripes of one to five inches (2 5 to 13 cm) in length and one quarter to one half of an inch (0 6 to 1 2 cm) in width Fresh striae are deep pink or purple the latter color not being due to hemorrhage as one might expect but to the transparency of the thinned skin In the early stage they look like the marks of whip lashes which in French are called vergetures This expression is occasionally used for striae Gradually the thin tran parent skin is replaced by a denser scar like tissue of pearly white color Sometimes old striae are brown with pigment Striae never disappear completely but they may

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*Stoddard[1653] found the 17 keto steroid levels in one of his cases to be 8 2 to 10 mg in the twenty four hour urine compared with the normal pregnancy range of 3 to 6 5 mg

[1653]Stoddard F J Hirsutism in Pregnancy Am J Obst & Gynec 49 417-422 1945

[1654]Hen 1 Hypertrichosis in Pregnancy Ztschr f d ges p r Med 104 182 1938

[1655]Afanassiesky I M Le diagnostic de la grossesse au debout par la réaction chimique des cheveux Gynecol gia i Acco heurstwo p 36 1934

[1656]Lombolt S Hypertrichosis an der Oberlippe und ihr Schwinden während der Gravidität Klin Wchnschr 13 10 7 10 8 1934

[1657]Halban J and Spitzer M Z Ueber das gesteigerte Wachstum der Nägel in der Schwangerschaft Monatschr f Geburtsh u Gynäk 82 5-31 1929

become quite inconspicous The surface of fresh striae is smoother than the normal skin sometimes slightly wrinkled transversely or diagonally so that diamond shaped figures are formed

Fig 214



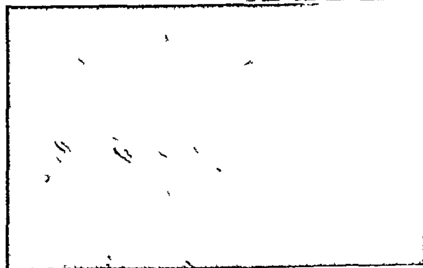


Fig 215

Fig 214 Striae of pregnancy
Fig 215 Old atrophic triae of pregnancy

The palpating finger receives the impression of emptiness and decreased resiliency This is caused by the lack of the elastic fibers the skin skeleton Some striae on the lower abdomen and the sides are raised and more palpable [16 8]

The striae caused by pregnancy are usually but not always symmetrical They are arranged in several groups One group of longitudinal striae surrounds the navel extending farther downward than upward A second less pronounced system occupies the lower abdomen its striae often crossing those mentioned before A third system runs longitudinally over the hips down to the thighs A fourth large group forms concentric and approximately circular figures around the sacral area This group may extend upward as far as the eighth dorsal vertebra Other mostly smaller bunches may surround the popliteal and elbow areas and cover the shoulders and axillary folds Their direction is longitudinal Finally the breasts show striae arranged in radial fashion around the areola [1458, 1581, 16 9, 1660] It should be kept in mind that striae are not always caused by pregnancy This fact is occasionally of some forensic importance Striae from obesity are mostly found in longitudinal groups on the upper arms hips and thighs Some surround the navel The striae produced by fast growth during adolescence run transversely They cross the thighs and to a lesser extent the hips and the lower back The striae following typhoid fever dysentery and other infections are most frequently found across the lower thighs just above the knees Generally striae develop in a direction perpendicular to the maximal tension If a limb grows longer the striae appear transversely if it increases in thickness the striae are directed longitudinally Irregular tractions produce irregular striae e g those one observes occasionally on the side of the chest opposite to a pneumothorax [1661]

Striae gravidítatis occur in at least 90 per cent of all pregnant women though in very different degree (Credé and many other authors after E Kehrer[1631]) These high figures were derived from observations on white European women Some but not all pigmented races for instance the women of Java and the negresses of West Africa are reported to develop striae only very rarely [1662] This may be partly due to racial peculiarities or to the massaging of the pregnant abdomen a custom which has found its advocates in the western world [1631] Barfurth claimed that fifteen to thirty minutes of daily gentle kneading of the abdominal skin prevents formation of striae This treatment is also supposed to bring about a better contraction of the abdomen after delivery The recommendation does not seem to have been widely followed

The *histology* of the striae shows that the lesion is situated in the deeper layers of the cutis There is a marked basophilic reaction and changes in the shape and texture or complete atrophy of the elastic fibers within the striae and an increase in the pathological fibers at the border of the lesion Here some of them look

[1658] Fontana O Pregna y Complications—Atrophic Stri Ann di o t t ginec 61 1 4– 1 54 1939

[1659] B Gnauer St R Atrophi d Haut In A t a d Zi 1 s Die Haut u 1 Geschlechtskrankheiten vol II Berlin 1935 Urban & Schwarzenberg pp 718–21

[1660] Oppenheim M Atrophi n Handb d H u Gk 8 500-716 1931

[1661] Comby J Un as d v getures thor ciques unilatérales Bull t mém Soc méd d Hôp d Paris 48 1008 19?

[1662] Stratz, C H Ueber Schwa g rschaftsstr ifen Zbl f Gynäk 26 431 191?

curled as if they had given way to the tension and snapped back. *Inflammation* has occasionally been noticed in the early stages. Like the blood vessels they are arranged in the direction of the tension. It seems as if the tension does much harm to the elastic and only little to the collagenic fibers. The microscopic findings can be interpreted as evidence of chemical as well as mechanical damage to the elastic fibers. Lately Fontana[16 8] has described striae with a marked inflammatory reaction and lack of distention as expressed by the normal wavy appearance of the papillae.

The microscopic evidence furnishes some support to the opinion of the majority of modern authors that the mechanical *tension*, however necessary it may be, is *not the only factor* in the pathogenesis of striae. This belief is based on a variety of observations. Some pregnant women develop striae in spite of relatively little tension; others never do no matter how extended their abdomens become. Of possible significance is the case of a pregnant woman who acquired striae over the biceps muscle of one arm from carrying books while the same exertion did not cause striation when she was not pregnant.

Tension does not always lead to striae. There are many cases of enormous cysts, ascites, and edema with extreme stretching of the skin but without striae. While the fat boys with Fröhlich's syndrome rarely show striation, the obese patients with Cushing's syndrome always have them, and just in this condition the striae not only are the widest ones one can observe but they are already very marked when obesity has not reached degrees which could easily explain cutaneous tears. In men striae are found in 6 per cent.[1663] Men are probably less apt to develop striae than women if one does not consider the striae of pregnancy. The pronounced striation in the basophile adenoma of the anterior pituitary and the pituitary changes in pregnancy suggest a pituitary hormonal factor. Pseudoxanthoma elasticum, which is clearly a disease of the elastic fibers, has been seen appearing in crops during two pregnancies of a patient.[1664]

The loosening effect of pregnancy on the elastic tissue of the pelvic ligaments, which is said to be of pituitary origin, may be caused by the same agent which has an affinity to the elastic fibers of the skin. The kyphosis which commonly develops in Cushing's syndrome may also be due to the same elastica loosening factor as the striae. In the cases of striae caused by adolescent growth the actual tension of the skin is not great compared with other conditions of stretched skin which do not lead to striation. Adolescence is a period of increased pituitary activity. Infections too may have a damaging influence on the elastic fibers. Striae are known to occur, though only in a small minority of the patients, mostly adolescents, after typhoid fever, dysentery, paratyphoid, *in the course* of typhus, rheumatic fever, leprosy, syphilis and other infections. Almost always the patients have been bedridden over a long period of time. In these cases the striae are found on the back and often above the patella, which may have something to do with lying in bed with the knees bent. In pulmonary tuberculosis

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[1663] Glaubersohn, S. A.: Contribution à l'étiologie des vergetures linéaires. Ann. de dermat. et syph. 8: 732-734, 1937.

[1664] Wiener, K.: Pseudoxanthoma elasticum und Gravidität. Zbl. 33: 357, 1933.

striae have often been observed on the side of the thorax opposite to the side of the main lesion Increased movement and coughing could explain this localization but this apparently well established fact was not confirmed in twelve ca es of striae thoracicae among 5 800 tubercular patients [1665] Szánto[1666] in his large series always found them on the side of the pulmonary involvement

Transverse striae crossing the spine below the level of the shoulder blades are relatively common in spondylosis deformans but are suppo ed to be rare in spondylitis [1667]

Several authors have tried to correlate the color of the hair with the forma tion of striae The results are contradictory which probably means that there is no relationship The older primipara is less apt to develop striae than the younger one The same is claimed of the more virile type[1668] and of the short asthenic megalosplanchnic women [1669 1670] The more striae a woman develops in pregnancy the more likely she is to suffer perineal lacerations but no relation to the labor pains has been established [1671] It is possible that a hereditary factor has influence on the development of striae Leven[167] saw lumbar striae in three of nine siblings and Siemens[1673] twice saw concordant striae in nulliparae who were identical twin sisters In the unique case of pregnancy of one of siamese twins the nonpregnant one did not develop striae (Hubner after Siemens[1673]) Hor neck[1359] observed the appearance of striae after the injection of adrenal cortical extract

The *elasticity* of the skin in normal pregnant women is about one third lower than normal This lack of elasticity is still more marked in the presence of clin ical edema and albuminuria [16 4 16 5] It starts in the third month and reaches its peak at the end of pregnancy Though edema may lower the elasticity of the skin it does not increase the tendency to formation of striae

Edema —A slight increase in the amount of fluid in the skin and in the subcutaneous tissue of the pregnant women must be considered normal This is to a large extent due to the retaining influence which estrogens and progesterone exert on sodium and water metabolism [1676] Surgeons know that the cleavability of the tissues is increased during pregnancy The butchers know that it is easier

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[665]Hamm r 1 Striae Distensae in the Skin of Consumptives Tubercle 2 349-352 19 1

[66]Szánto C Endokri tedingte Dermatos n bei Lu gentuberkulös n Zbl 40 734

[667]Satke O and Winkl W Striae distensa cutis I Wi n Arch f i n Med 29 351 38 19)

[668]S ynsch I S hwang rschaftsstreifen und Konstitution Zbl f Gynäk 60 1749 17 8 19 6

[1669]Nardelli L Il p obal lle fatto e docri o nella patog nesi d lle st iae cutis atrophicae Endoc inol p tol con tit 1 61 70 19 6 Zbl 22 516

[670]Nard lli L Le tria cuti atrophi ae Gior ital di dermat e sif 76 607-6 7 1935

[7] Bodecurt M Stri e gra idarum A ch f Frau nk 14 199 06 19 8

[672]Lev n Streif nz ichnung d r Regio sacro-lumbali Dermat Wchn ch 91 333-336 193

[1673]Si m ns H W Die Vererl ung in der Aetiologi d r Hautkrankh it n Handb d H u Gk 3 1 160 1931

[1674]Decio C Al une ri erche di lastom tria cutan a nel campo o t t ico-ginecologi o Ri ital di ginec 11 534-546 1930 Zl l 38 310

[1675]Ans lm, F t t das V rhalten de Haut lastizität währ d d r Schwang schaft Diss 1930 Frankfurt a M Zbl 41 70

[1676]Taylor H (Jr Warn r B C a d Wel h L A Relati ship of E t ogens an l Progesterone to Edema of Normal and To mic Pregna cy Am. J Obst & Gynec 45 547 568 1943

to skin a pregnant animal than a nonpregnant one. Both observations may be explained by the serous imbibition of the tissues.

While a certain pre-edematous condition is physiological in pregnancy, clinically noticeable edema of the legs occurs in 28 per cent of all pregnancies (Hoffner after Scheuer[1663]).

McClure and Aldrich's *method of testing the skin for impending or not yet palpable edema by measuring the disappearance time of a welt produced by the intracutaneous injection of 0.2 c.c. of 0.8 per cent NaCl solution showed that in pregnancy the disappearance time is almost always shortened.*[1677] *The reduction of the disappearance time is in direct proportion to the degree of edema and can be used as a prognostic sign.*[1677,1679] *The disappearance time is shorter in the legs than in the arms.* It is considered to be an unfavorable sign suggesting impending eclampsia if the stasis of a pregnant woman does not disappear on bed rest.[1680]

Severe edema of the vulva is a rare complication of pregnancy, being encountered three times in 12,000 pregnancies. The trouble may repeat itself in subsequent pregnancies. The swelling may reach the size of a man's head and may even necessitate cesarean section.[1682,1683]

Circulation.—During pregnancy the peripheral circulation is marked by *vasomotor instability*. Pallor, quick changes in the facial color and sensations of heat and cold in the extremities are common, particularly in the later months. Red or white dermographia is almost always noticeable though varying in intensity.[18,7,1683] This widely held opinion has lately been contested (Piccone after Vignes[1684]). Dermographia is most noticeable on the back, the sternal area and on the abdomen above the fundus uteri.[1449,1685] The reaction is reported to be weaker in heavily pigmented skin.

Direct observation of the peripheral blood circulation by *capillaroscopy* has shown that the flow of blood in the capillaries of the lower legs and of the fingernails is often slowed down. Segmentation or complete stasis or even regurgitation of the blood from the venules to the arterioles has been observed more often than in controls.[1654,1686,1688] It is considered to be an unfavorable prognostic

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[1677]Oblat n J: Die Quaddelreaktion als Frühdiagnosticum der Schwangerschaft. Arch. f. Gynäk. 133: 163-17 19 8.

[1678]Lash A F: Intradermal Salt Solution Test in Normal and Toxemic Pregnancies. Surg. Gynec. & Obst. 43: 40-60 1926.

[1679]Hornung R: Das Verhalten d. intracutanen Normosalquaddel bei Schwangeren. Zbl. f. Gynäk. 51: 773 30 19 7.

[1680]Hinselmann H: Über das Ödem der Schwangeren. Zbl. f. Gynäk. 45: 1301-1303 19 1.

[1681]Kamik H: Elephantiasis vulvae und Schwangerschaft. Zbl. f. Gynäk. 82: 0 1 0 3 1930.

[1682]Novak E: Vulva Ödem. Magy. Nögyogy. 6: 5 1937. Zbl. 86: 543 1937.

[1683]Jordan A: Hautveränderungen bei Schwangeren. Zbl. 8: 369.

[1684]Vignes H: Pregnancy Complications. Evolution of Varices in Pregnancy. Arch. d. mal. du coeur 32: 478-490 1939.

[1685]Piccone: Il dermografismo nella madre e nel neonato e relativi correlazioni ... Atti d. ... Acad. ... Siena 2: 571-591 1931.

[1686]Hinselmann H: Capillarbeobachtungen bei normalen und hydropischen Schwangeren. Zbl. f. Gynäk. 45: 16 19 1.

[1687]Hinselmann H, Haupt W and Nettekoven H: Beobachtungen und Aufzeichnungen ... der Angiospasmen bei hypertonischen Nierenkranken Schwangeren. Zbl. f. Gynäk. 45: 603-609 1921.

[1688]Hinselmann H and Haupt W: Über die Capillarbeobachtung bei Schwangeren. Med. Klin. 17: 370-371 19 1.

sign if the stases do not completely disappear on changing from the upright to the horizontal position [1686] In edema and with high sedimentation rates stases are pronounced In hydramnion a tortuous appearance of the capillary loops has been noticed [1689] It should be emphasized that stases of course are not a symptom of pregnancy They are the expression of an impaired peripheral circulation and occur in many conditions The number of capillary loops increases in two thirds of the pregnant women after the second month but not infrequently only as late as in the seventh or eighth month (Vinigradova after Melbard[1690])

Two months after delivery the normal number of hair pin type capillary loops is usually found again

The high *permeability* of the capillary wall is shown by the fact that the tourniquet test is positive in 80 per cent of the pregnant women [16 7] The serum of blisters produced by cantharides on the skin of pregnant women contains three to four times more lymphocytes than under normal conditions This observation can be interpreted as evidence of the higher endothelial permeability [1691] Other studies of cantharides reactions[169?] showed opposite conclusions

Pregnancy is by far the most frequent cause of *varicose veins* in women Only about 3 per cent of the women patients of a large varicose vein clinic had their trouble before their first pregnancy [1693] The incidence figures given by a number of authors vary within wide limits but 50 per cent does not seem too high They most often involve the lower legs only with a preference for the right side In almost 20 per cent of the pregnant varicosities of the vulva may produce large bluish tumorlike convolutions

Hemorrhoids are almost as common as varicose veins of the vulva

The most simple explanation of the varicosities of pregnancy is the pressure of the uterus on the large pelvic veins However this cannot be the only cause since varicose veins sometimes develop in an early stage of pregnancy when pressure is negligible They sometimes appear as an early symptom of pregnancy soon after the first missed menstruation (Balard and Mehon after Vignes[1684]) Even at the common time of appearance in the third month the pressure of the uterus does not give a very plausible explanation since uteri of equal size with tumor hardly cause varicose veins Other observations[1684] can be interpreted against the purely mechanical pathogenesis The varicose veins of pregnancy often appear in crops and the temperature over newly developed varicosities is up to four centigrades higher than over older ones and over the symmetrical skin [1694] It is interesting that large intra abdominal tumors may cause edema but rarely varicose veins The elastic fibers in the wall of the varicose

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[1]F ll M Graviditätsdermatosen Endokrinologie **17** 391-391 1936

[1690]M llard S M Val ur di gn tique d la capillaroscopie dans la gros ess t d ns la s psi pu rpérale Gynéc t Obst **37** 00- 09 1938

Spi gl R Ca thaiidenreaktion u d Schwang rschaft Monatschr f Geburt h u Gynäk **78** 47-53 19 8

[1691]l t rs W F a d Lash A F P rméabilité des capillaires cut nées p ndant la gestation Arch Int Med **39** 1 18 19 7

[1693]M Dau l nd A M Varicose V ins in Pr gnancy West J Su g **47** 81 84 1939

[1?] tübel A V ricen und Schwa g rschaft Med Klin **17** 13 7 1921

The outbreak of the disease is often preceded by premonitory itching without visible changes other than a few wheals. Often in this prodromal period nausea, headache and fever may be observed but lack of uniformity characterizes this phase just as much as the later stages. The rash hardly ever breaks out on large surfaces. Usually in one or a few areas, e.g. around the navel and on some parts of the arms, erythematous patches appear which lead to the fully developed *syndrome*. Wheals, prurigo-like small papules, vesicles, pustules, groups of blisters and bullae appear in crops and create a rather polymorphic picture. While at times erythematous and urticarial lesions predominate, in other periods the abundant bullae may present a pemphigus-like aspect. In some cases aggregated scratched small papules on the trunk and on the extremities resemble prurigo Hebra. This dermatosis has been described as a separate dermatosis under the name of prurigo gestationis.[1702] It is probably only a variety of the highly polymorphic herpes gestationis.[1703] Everybody who has observed cases of dermatitis herpetiformis over a long time knows that such prurigo-like stages occur. However, the separation of prurigo gestationis from herpes gestationis is still stressed by some authors.[1640]

The erythematous and vesicular patches of herpes gestationis often spread centrifugally leaving annular or gyrate lesions with accentuated edges and red scaly or pigmented centers. There is little tendency to involve the mucosae. Ulceration does not occur and no scars develop unless severe pyogenic infection complicates the course. Besides the discomfort of large oozing surfaces, in some cases the main complaint of the patients is the furious itching, burning, stinging or pain which accompanies the crops. The attacks of pruritus in particular which can be provoked by various causes, especially psychic excitement, can make the condition of the gravid woman a most miserable one. It needs all the efforts of dermatological and psychological treatment, and in particular the assurance of complete recovery without disfigurement, to keep up the morale of the patient.

The eruption affects the extremities more often than other regions but no part of the body surface is sure to remain free. The nailbeds may become infected and the nails may be shed. The outstanding histological feature is the eosinophilia in the blister serum and in the tissue, particularly in perivascular infiltrations. Blood eosinophilia is common too. Eosinophilia, especially in the tissue, *though not being specific*, frequently accompanies allergic diseases and therefore suggests an allergic nature of the dermatosis.[189] The recession of the blood eosinophilia is considered a favorable prognostic sign.[1704]

The relationship to pregnancy is, of course, an outstanding characteristic of the disease. Though occasionally an early symptom of pregnancy, herpes gestationis has been seen to appear most often in the second half of pregnancy.[1703] If there are attacks in subsequent pregnancies the onset may be earlier each time

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[1702] Besnier, J.: Sur la question du prurigo. 3rd Internat. Congr. of Dermat. London 1896.
[1703] Rieck, F.: Herpes gestationis. Handb. d. H. u. Gk. 7/?, 637-651, 1931.
[1704] *Fliasch, ff. O.: Sur la valeur de l'éosinophilie dans les dermatoses bulleuses et spécial m... t dans la d...rmatite h...rpétiforme d...* Duhring. ...ang 2: 1-3, 1928.

and the disease may become more severe[1703 1705 1707] Besides this most common type other relations to gestation occur Some pregnancies may remain free and only in a later pregnancy will the first eruption occur (Puente Gross in discussion to Rostenberg[1708]) A normal pregnancy may be had between pregnancies with herpes gestationis[1709] The onset may be very late in the last days of pregnancy[1708] or even in the puerperium The disease may break out during pregnancy improve or heal with the approaching delivery and then be followed by a severe crop during the puerperium[1710] Characteristically herpes gestationis does not remain after pregnancy as an ordinary dermatitis herpetiformis In a few cases menstrual recurrencies have been observed[1711 1 1] So far unique is the case of herpes gestationis caused by choriocarcinoma two years after a pregnancy with hydatidiform mole[1713]

The prognosis is favorable for the mother A fatal outcome is rare and may be caused by sepsis rather than by the dermatosis itself (Schonfeld after Riecke[1703 170 1714 171])

The prognosis for the child is unfavorable Stillbirth ends about fifty per cent of the pregnancies complicated by herpes gestationis[1706] Babies born alive died in several instances from infection during the first year[1703 1 06] Skin lesions in the living or dead child possibly pertaining to the dermatosis of the mother have been reported[1 83 1700 1711] but the evidence of true connatal herpes gestationis is not convincing[1703]

The etiology and pathogenesis of herpes gestationis is not much better understood than that of dermatitis herpetiformis It is just the connection with pregnancy which suggests some explanation Toxemia of pregnancy with damage to the liver to the kidneys and to the skin has often been accused The nitrogen content of the urine is reduced during the eruption and increases with recovery Just as in dermatitis herpetiformis eruptions may be precipitated by internal or percutaneous application of potassium iodide (Jadassohn s test) However this phenomenon is not constant Endocrine secretions may as in the case of impetigo herpetiformis provide a better explanation than those given today Rostenberg[1 08] in his case found the anterior pituitary like principle increased in the urine twenty six days after delivery In Elliott s[1713] case of herpes gestationis caused by choriocarcinoma the pregnancy tests were strongly

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[1705]Heckert E Ein Fall von H rpes gestationis mit tötlichem Ve lauf Geneesk. Tijd chr v Ned rl Ind ll 68 1094 1095 19 8 Zbl 31 57

[1706]Howard R Herpes Gestationis Arch Dermat & Syph 28 78 1933

[1707]Madd n J F Herpes gestationis Arch D rmat & Syph 32 550 1935

[1708]Rost nb rg A Herpes gestationi Arch D rmat & Syph 30 736 1934

[1709]Sechi F Co tri uto allo tudio dell h rpes g stationis Glor ital di dermat e sif 73 1353 13 2 193

[1] Lue t J J and Bonfigli II H Polymo ph Schwangerschaft d rmatitis Rev argent de mato sif 18 211 193 Zbl 42 475

[1] Tommasi L Contri uto alla cono cenza dell h rpes gestationi Glor ital d. mal ven 65 840 88 19 4

[1] Crosti A H rpes gestationi e d rmatiti polimorf doloros (Duhring Brocq) Glor ital di dermat e if 73 15 174 193 Zbl 42 85

[1] Elliott J A Bullous Dermatoses of Toxic Origin Case Involving an Association With Choriocarcinoma Arch De mat & Syph 37 219 233 1938

[1] obajima W Ein Fall von Herpes gestationis Jap J De mat & Urol 33 43 1933 Zbl 45 01

[1] Gellhorn G Ecz ma in Pregnancy Am J Obst & Gynec 26 408 1933

positive The relationship of dermatitis herpetiformis to ovarian function however inconstant and contradictory it may be cannot be easily dismissed in view of the considerable case literature.[1703] However there still is no satisfactory endocrine explanation. Some evidence points to allergy. The repeated occurrence in pregnancies with each subsequent attack starting earlier and taking a more severe course has its parallel in acquired allergy. The urticarial element in the eruption and the marked eosinophilia in the blood blisters and tissues lend support to an allergic hypothesis. Passive transfer has not been successful.[1713] *A hormone may well act as an allergen*. Tommasi[1711] suggests the corpus luteum; such autogenous allergies are known. Infection as a cause can neither be denied nor as yet be proved. Thus the pathogenesis of herpes gestationis as well as that of dermatitis herpetiformis remains unknown.

Based on the hypothesis that herpes gestationis is caused by toxemia and the inability to produce neutralizing antibodies Mayer and Linser[1716] inaugurated *the treatment of herpes gestationis with intravenous injections of 10 to 20 c c* of fresh serum of normal pregnant women. With this method Seitz cured 37 out of 38 cases of the various dermatoses of pregnancy. This method is still widely applied. In some countries this serum is available in ampoules. The serum of pregnant mares has been successfully used too. In spite of successes *the theoretical foundation of the treatment with normal pregnant women's* serum however has become untenable because of the equally successful treatment with normal serum, horse serum and especially with Ringer's solution. Riecke[1708] gives the following formula for this mixture:

Sodium chloride	1 8
Calcium chloride	0 018
Potassium chloride	0 084
Sodium bicarbonate	0 06
Aq distill ad	200 0

This solution is injected intramuscularly or subcutaneously in doses of 150 to 200 c c. Similar success has been achieved with serum or blood from the umbilical cord, with the patient's own blood[1717] and with milk. In the published cases one or the other of the above mentioned methods, especially the normal pregnant women's serum, has helped. *One may surely assume however that failures of the therapy have not been reported with the same zeal as the successes*. Only a few of the observers have seen a considerable number of cases of this rare disease, and the often irregular course of the dermatosis *should be remembered in evaluating any method of treatment*. Lately contradictory reports on the sulfonamides have appeared.[1714, 1719] Ovarian extract,[1711] corpus luteum[1709] and Viosterol[1715] have also been advocated.

[1716] Mayer, A., and Linser, P.: Ein Versuch, Schwangerschaftstoxikosen durch Einspritzung von Schwangerschaftsserum zu heilen, Münch. med. Wchnschr. 57: 2757-2759, 1910.

[1717] Watrin, J.: Dermatite polymorphe douloureuse et autohémothérapie, Bull. Soc. franç. de dermat. et syph. 21: 41, 1914.

[1718] Turner, S. J., and Zakon, S. J.: Herpes Gestationis, Am. J. Obst. & Gynec. 41: 525-527, 1941.

[1719] Lewis, G. M.: Herpes Gestationis: Successful Treatment With Sulfathiazol, Arch. Dermat. & Syph. 46: 881, 1942.

Purpura.—It has already been mentioned that pregnancy increases the permeability of the capillary wall and that the tourniquet test (Rumpel Leede phenomenon) is often positive. Spontaneous petechiae are occasionally seen under the strain of labor. More severe purpuric rashes have been observed,[1720] some of them with dangerous hemorrhagic complications. They are generally considered toxic. They disappear after delivery[1453] but sometimes recur in subsequent pregnancies, in some cases in the same spot as a fixed eruption.[1721] Rushmore[1722] has collected forty seven cases, mostly of severe purpura in pregnancy. The mortality of the mothers as well as of the children exceeded fifty per cent. Some cases have the character of thrombocytopenic purpura.[1723] Pregnancy may activate dormant thrombocytopenic purpura or cause the first manifestations of the disease. Besides purpuric skin lesions of great variety in size, severe, even fatal hemorrhages from the nose, the gums and other sites may occur. If treatment fails, termination of the pregnancy is indicated. Bruise like hemorrhagic discolorations of the abdominal wall in and about the umbilicus occur in ruptured extrauterine pregnancy and other intra abdominal hemorrhages. This is known as Cullen's sign.[1724]

Miscellaneous Eruptions.—It would be monotonous to describe all the rashes which have been observed in pregnancy other than the well characterized dermatoses. There are morbilliform erythemas, sometimes with eczema or with pruriginous papules. Erythema exudativum multiforme[1725, 1726] is also on record. Its differentiation from herpes gestationis is difficult in some cases. Urticaria of pregnancy, angioneurotic edema and lichen urticatus are known. Pruritus of pregnancy is common and sometimes of a severity which may cause abortion.[1449] Eczema,[1615] lichenoid multiple lesions resembling localized prurigo,[1727] pemphigus vulgaris,[1728] scleroderma,[1729, 1730] cutaneous atrophy in spots (Temesvary and Oppenheim after Novak[1451]) and other conditions have occasionally been seen during pregnancy, sometimes repeatedly, and usually healing after delivery. Selitzky[1640] described toxic symmetrical dermatitis. It has been said that the pregnant woman has a marked tendency to develop drug eruptions.[1731] Pruritus vulvae and vulvitis of pregnancy is often caused by monilia but is rare compared with

[1720] Kaiser K. Seltene Hautveränderungen bei Schwangeren. Med Klin 24 933 934 1928
[1721] Vignes H and Stiassnie. Purpura récidivant au cours de trois gestations successives. Progrès méd 48 167 168 19 1 Zbl 1 498
[1722] Rushmore S. Purpura Complicating Pregnancy. Am J Obst & Gynec 10 553 590 1925
[1723] Batizfalvy J. Pregnancy Complications—Thrombopenic Purpura. Ztschr f Geburtsh u Gynäk 119 65-95 1939
[1724] Cullen T S. Bluish Umbilicus as Diagnostic Sign in Ruptured Extrauterine Pregnancy. Contributions to Medical and Biological Research etc. New York 1919 Paul B Hoeber pp 4 0-4 1
[1725] Gross P. Erythema multiforme gestationis. Arch. Dermat & Syph 23 567 1931
[1726] Ebert. Toxic Eruption of Pregnancy Multiform Erythema Type. Arch Dermat & Syph 16 509 510 19
[1727] Davies J H T. Prurigo Annularis. Brit J Dermat 53 143 145 1941
[1728] Klopstock. Pemphigus vulgaris Associated With Pregnancy. Dermat Ztschr 40 305 19 4
[1729] Anselmino I J and Hoffman F. Ueber Sklerodermie und Schwangerschaft. Ztschr f Geburtsh u Gynäk 103 60-66 103?
[1730] Girard. Cas d sclé od mi n banies à la suit d une grossesse. Troubles ovariens. Le Scalpel 2 815 19 9 Zbl 32 78
[1731] Rosenfeld R. Skin During Pregnancy and Puerperium. Urol & Cutan Rev 48 86-88 1944

the frequent occurrence of yeasts in the vagina of pregnant women.[1733] The typical monilia vulvitis causes itching and redness of the introitus and of the vagina. Yellow specks of thrush which are not easily removed without bleeding contain the mycelia. Vaginal thrush caused by *Monilia albicans* was found in 25 per cent of 200 consecutive pregnancies having leukorrhea in Edinburgh, Scotland.[1734] It is advisable to look for vaginal thrush in order to safeguard the baby from infection at birth. Very little is known about the cause of the more severe ulcerations of the external genitalia in pregnancy which have occasionally been seen.

Stimulation of Growth.—Symmetrical *erythema of the palms*, mainly on the thenar, hypothenar and finger tip eminences, has been described in connection with a variety of internal conditions, notable among them being cirrhosis of the liver and pregnancy. The erythema usually leaves the triangle shaped center of the palms pale. The condition is often associated with multiple, sometimes pulsating, spider like *telangiectases*.[1735, 1736] The erythema as well as the telangiectases often vanishes after parturition. In some cases the spiders result in actual hemangio-endotheliomas which may even become locally malignant and infiltrating.[1737]

Preexisting and apparently stationary hemangiomas may start to grow during pregnancy.[1738]

Fibroma molluscum gravidarum[1739, 1740] is an eruption of small, soft, pedunculated or sessile, sometimes pigmented fibromas which appears in crops during the latter half of pregnancy and disappear after childbirth. The little growths appear especially around the neck and in other areas where skin rubs against skin, e.g., under pendulous breasts and in the axillary folds. They may be associated with large brown spots so that a close resemblance with Von Recklinghausen's disease results, including the microscopic anatomy. The lesions which appear during pregnancy usually[1741] but not always[1742] disappear after delivery. While the widespread or even universal types of fibromatosis gravidarum, as it should be called,[1743] are rare, a crop of some cutaneous tags[1744] around the neck is common in pregnancy. Pregnancy stimulates the growth of *skin cancer*

[1733] Waters, E. G., and Cartwright, F. W.: Significance of Vulvovaginitis in Pregnancy, J. A. M. A. 113: 30-31, 1939.

[1734] List, W. C., and Cruickshank, L. C.: On Thrush, Special Reference to Vaginal Thrush, Edinburgh M. J. 47: 463, 1940.

[1735] K... al, F.: E... ntielle T... la... gi... kta... ien bei Gra... idität, Zbl. 87: 74, 19 5.

[1736] Walsh, F. ..., and Becker, S. W.: Erythema Palmare and Nevus Araneus-like Telangiectasias, Arch. Dermat. & Syph. 44: 616, 1941.

[1737] Urbach, E.: ... Teleangiektasien, Zbl. 18: 339, 19 6.

[1738] Davis, ... M.: Subcutaneous Hemangioendotheliomas ... Pregnancy, J. Obst. & Gynaec. Brit. Emp. 45: 66 ..., 1938.

[1739] Urbach, E.: ... Hämangiek... tasien ... Angioma ca... rnosum ... Schwangerschaft u. ... Menstruation, Zbl. 28: 18, 19 ...

[1740] Brickner, S. M.: Fibroma Molluscum Gravidarum, Am. J. Obst. & Gynec. 62: 191-195, 1906.

[1740] Brickner, S. M.: Molluscum Fibrosum Gravidarum, Am. J. Dermat. & Genito-Urin. Dis. 16: 240, 1912.

[1741] Burg, E.: Über das Fibroma molluscum gravid... Zbl. f. Gynäk. 61: 73 ..., 39, 1930.

[1742] Ward, E.: Multiple Pigmented Warts in Pregnancy, Brit. J. Dermat. 24: 153, 1913.

[1743] Fischl, F.: Über d... E... uss d... Schwangerschaft auf das Auftreten und Wachstum gut... rtiger Geschwülste, Wien. med. Wchnschr. 83: 645-648, 1933.

[1744] T... mpleton, H. J.: Cutaneous Tags of the Neck, Arch. Dermat. & Syph. 33: 495, 1936.

produced in rabbits by the application of carcinogenic tar fractions[174] The growth stimulating effect of the estrogens is suggested as a cause The hyper cholesteremia of pregnancy makes one expect a rather frequent occurrence of

Fig 216



Fig 217

Fig 216 — Fib oma of p egnancy

Fig 217 Fibroma (skin tags) of pregna cy These little tumors may app ar early in pregna cy and som may r ach larger ize

lipoidoses It is surprising that xanthoma and xanthelasma in connection with pregnancy is rare (author s case see also Schaaf[1818]) Growth stimulation may also be the cause of the so called gingivitis hypertrophica of pregnancy This

[174] Krotkina N Ueber d n Einfluss von Graviditat und Lactation auf di du ch Teerpin lu gen erzeugten Epith lwuch rung n am K ninch nohr Ztsch f Kreb forsch 21 450-457 19 4

disorder[1746, 1747] frequently starts in the third month. In the early stages the gums are red and bleed easily. Then they swell, especially at the margin. The bulging edge may develop folds which cover the teeth and cause considerable trouble. If this hypertrophic stage is restricted to a small area, an epulis-like nodule may result. The term epulis gravidarum which has been used is misleading because of the different character of the two conditions. However, true epulis occasionally starts in pregnancy and the growth of a preexisting epulis (Seitz) or giant cell sarcoma[1747] may be stimulated. The swelling of the gums disappears quickly after delivery, sometimes within a week. Gingivitis hypertrophica of some degree is seen in more than half of all pregnant women. In 32 per cent the condition was moderately severe and in 4 per cent severe.[1748] These figures were observed in Germany and may well differ from those of other countries.



Fig 218 — Xanthelasma started in pregnancy

This gingivitis of pregnancy is primarily a connective tissue hypertrophy. The inflammation seems to be secondary although it may dominate in the fully developed case. It has been shown that similar hypertrophy of the gums can be produced in monkeys by injection of the concentrated urine of pregnant women.[1749] Huber[1750] found a high level (*700 M U*) of follicular hormone in one liter of urine of a twelve-year-old boy who suffered from hypertrophy of the gums. Newborn children often show a comparable succulence of the oral mucosa which disappears within a few days leaving the empty suckling folds. This may be one of the effects of the maternal or placental hormones. Vitamin C deficiency and hypocalcemia are accused by other, mostly European, dentists of being the main cause of gingivitis in pregnancy. The proponents of this theory base their opinion on the low content of vitamin C in the serum of pregnant

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[1746] Portier J Gingivitis in Pregnancy Union méd du Canada 65 545-546 1936
[1747] Monash S Proliferative Gingivitis of Pregnancy Cases Arch Dermat & Syph 24 580-586 1931
[1748] Schuck J Schwangerschaftsgingivitis und ihre Behandlung mit Kalk und Vitamin C Arch f Gynäk 169 571-578 1939
[1749] Ziskin D Blackberg S and Stout A P The Gingivae During Pregnancy Surg Gynec & Obst 57 719-726 1933
[1750] Huber H Zahnfleischerkrankungen in der Schwangerschaft Zbl f Gynäk 62 1977-1981 1938

women suffering from gingivitis compared with normal controls and on the therapeutic effect of vitamin C

Many dentists advise treatment with Vitamin C and calcium It is claimed to be helpful if the process is not too far advanced [1748,1751] The teeth should be cleaned checked and treated at the beginning of pregnancy in order to minimize secondary infection Only complications require local treatment

The treatment of the dermatoses of pregnancy is both topic and systemic The former is determined by the type and stage of the lesion In the vast majority



Fig 219 S re a eruption in pregna cy There wa alm st no ac e p sent before

of the ca es it is possible to keep the patient comfortable or to heal the eruption even during pregnancy In the more severe and of course the dangerous cases the treatment should follow the methods de cribed under herpes gestationis Ringer s solution should always be tried first since it is not connected with any risk Its antipruritic effect has been praised [1,52] Injection of 1 to 5 c c of the

[17] Brauer R Pregnancy Complications Gingivitis Med Klin 35 250- 51 1939

[1,52] Sala S L and Castell os S F Treatm nt of Pru it of Pregnancy With Ringer Solution S mana méd 2 161 165 1937 211 68 645 1938

patient s own blood has also been recommended [1753] The serum of normal preg nant women should be given if Ringer s solution fails In these cases the ques tion of the artificial termination of the pregnancy will arise In herpes gestationis the prognosis is favorable for the mother and less so for the child These cases will rarely require the termination of the pregnancy If the diagnosis of impetigo herpetiformis is made the pregnancy should be interrupted as soon as possible before large areas become involved and infected and make the operation dan gerous Even early abortion does not secure an absolutely favorable prognosis [1286]

Influence of Pregnancy on Existing Dermatoses —Pregnancy often influences the course of existing dermatoses The observations regarding *psoriasis are contradictory but improvement during pregnancy occurs quite* often The same is said of *acne* (Kaufmann in discussion to Seitz[1627]) but here too the observations are conflicting [1639] The author has seen at least two cases of acne conglobata with severe exacerbations during pregnancy

In several strikingly parallel instances patients with *alopecia* areata totalis regained their hair during pregnancy only to lose it again a short time later [14] Seborrheic alopecia usually improves or is arrested

Some contrasting observations on scleroderma and pregnancy have ap peared (Jadassohn in Wiener[14 3 1465 1689 17 9]) (See scleroderma)

Von Recklinghausen s disease often takes a turn for the worse in pregnant women [1754]

[1753] Lysander A Behandlung d r Schwangerschafts Dermatosen Svenska läk tidning 31 33 39 1934 Zbl 49 151

[1754] Sharpe J G and Young R H Neurofibromatosis Effect of Pregnancy on the Skin Mani festions J A M A 106 682-693 1936

Chapter XXIV

CHILDBIRTH AND PUERPERIUM THE SKIN IN THE NEWBORN

Childbirth and Puerperium

Emphysema —In rare instances the intrathoracic pressure caused by the labor pains can puncture the lung tissue and press the air under the visceral pleura along the mediastinal spaces to the neck Once such an air channel is formed more and more air is pumped into the loose connective tissue Finally the subcutaneous tissue becomes inflated and painful and gives the palpating finger the crepitant sensation found in some chest injuries and in gas gangrene The first symptoms of subcutaneous emphysema are most frequently found in the face less often in the nape of the neck or above the sternum[175] Some authors feel that the phenomenon is better explained by rupture of the tracheal wall due to the intense vibration caused by screaming Pleural adhesions are also believed to play a part[1756 1757] Only very rarely has an actual laceration of lung tissue been verified at autopsy (Depaul after Scheuer[143]) Even laceration of the buccal mucosa with ensuing emphysema has been observed[1755 1756] The clinical picture of the frog like inflated neck from where the emphysema may travel long distances under the skin must be impressive but even very experienced obstetricians have encountered it extremely seldom about once in several thousand confinements The patients were almost exclusively primiparae with pelvic contraction and very large babies The prognosis of the emphysema per se is usually favorable

Petechiae —Since pregnancy creates a purpuric tendency it is not surprising that under the strain of labor petechiae appear They are most often seen in the conjunctivae and on the neck and shoulders rarely over the entire body[1757 1758]

Urticaria —Urticaria beginning with labor and disappearing two days later has been seen *

Pruritus[1759] and *Herpes* occur occasionally in the first day of the puerperium

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J Jadassohn personal communication (also author s case)

[1755] Kosmak G W Cutaneous Emphysema During Labor Bull New York Lying in Hospital 1907 Abstr Zbl f Gynäk 32 10 8 1908

[1756] Briad Iro D Cervicothoracic Subcutaneous Emphysema Cas R v de ginec e d obst 2 19 195 191

[1757] Stoeckel W Tratado d Obst ed 2 Vol I p 207 1932

[1758] Stubbs J B and Martin H F Traumatic Purpura Occurring During Labor J Obst & Gynaec Brit Emp 40 30 -304 1933

[1759] Simunich W A Postnatal Complaints in 1000 Consecutive Cases Illinois M J 74 5 6-661 1938

Nail, Hair —Not all the dermadromes of labor become immediately apparent The great event leaves its mark on the growing tissues of the nails and hair, but it is only considerably later that these sequelae become evident From twenty-one to forty two days after the delivery transverse grooves or lines very rarely only white stripes may appear on the proximal ends of all fingernails or on some symmetric nails These lines which are known as *Beau s lines* are more pronounced on the nail of the thumbs and the first fingers than on the smaller



Fig 220



Fig 221

Fig 220 —Hoof of an old cow showing periodical line formation (Courtesy University of Wisconsin, D partm nt of Dairy Husbandry)

Fig 221 — Horn of an old cow Physiological ring formation in regular intervals xcept on the free end which represents the oldest part of the horn formed duri g the first years of lif The rings become less distinct the older they are (Courtesy University of Wiscon in D partment of Dairy Husbandry)

fingers They are not always present but they are quite common They may occur after any acute disease and after gastrointestinal cardiac and other attacks Therefore they alone cannot be regarded as a certain indication of preceding childbirth Since it takes about thirty days for the nail to appear under the edge of the cuticle and since the nail grows about 0 1 mm a day it seems easy to calculate retrospectively the day of delivery But individual differences in the rate of growth and other factors make a more accurate determination than the week of the event impossible [691]

Beau s lines also appear on the nails of the newborn (see newborn) Comparable to Beau s lines of the human nails ring formation on the horns of cows

after calving are commonly observed and used as an indication of age Similar marks are known to occur on the hooves of mares *

The growing *hair* is affected by the trauma of childbirth just as is the nail A considerable number of hairs are so weakened that they fall out after two to three months Other hairs show only a thinned portion of varying length (Pohl Pinkus mark) If the puerperium is complicated by fever and infection the mark may involve a longer stretch This mark is not only thinner but also lighter in color Considering the daily rate of the head hair growth as 0 3 — 0 5 millimeter or approximately 1 cm per month[148] it is possible to determine the day of the delivery within certain limits If several pregnancies follow each other closely the hair does not have enough time to recover and stays thin and short Some veterinarians believe that animals who are prevented from eating the placenta lose much hair [1761] even to the degree of complete epilation Gross advises administration of 5 gm of placental extract three times daily for the treatment of post partum hair loss in women His series of 24 patients afflicted with a condition which offers a good prognosis anyway needs confirmation on a larger scale

Skin irritations from the lochia and dermatitis around the nipples shall be mentioned for the sake of completeness Simunich noted in one thousand consecutive cases the following postnatal complaints concerning the skin five cases complained of pruritus four of which involved the extremities only one the vulva There were four cases of excessive perspiration and four cases of herpes between the second and seventh days In seven cases the axillary glands were swollen Reports of infections of many kinds [176] and onset of chronic diseases are numerous but no characteristic dermatoses seem to have been described in relation to this phase Puerperal sepsis may exhibit itself in erythematous morbilliform scarlatiniform and other rashes Exfoliative dermatitis probably caused by Staphylococcus aureus hemolyticus has been seen [1763] Purpura occurred also in the course of puerperal complications Sensitization of a woman to her own milk with allergic symptoms like urticaria and angioneurotic edema is considered possible though still lacking confirmation [1764]

The dermatoses of pregnancy usually subside in the postnatal period but *exacerbations in the early puerperium* are especially characteristic of herpes gestationis

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* There are two types of ring formation on the horns of cattle Normally rings appear at the base of the horn in both sexes every year after the third year It seems that they are caused by seasonal change of food Besides this physiological ring formation any event which depresses the metabolism of the animal deeply enough may leave its mark on the growing horn Such events may include disease nutritional change and also pathological births The normal births do not seem to cause rings Analogous phenomena are important in the hair of sheep Submaintenance nutrition causes thinning of the hair even to such an extent that the hair breaks off and the fleece may become lost (Personal communication from Prof E H Hze Department of Dairy Husbandry University of Wiscon in) (See also J H H r [60])

[1761] H ll r J Ti rde matosen Handb d H u Gk 14 1 719-937 1930

[76] Gross F R Dermatology in Relation to Endocrinology Clinics 2 813 833 1944

[763] D Lee J B Th Principles and Practice of Obstetrics ed 7 Philadelphia and London 1938 W B Saunders Co

[1763] Bin1 r A Exfoliative Dermatitis Due to Staphylococcus Aureus Hemolyticus During Puerperium Zbl f G burtsh u Gynäk 65 371-377 1939

[1764] Duke W W Allergy Asthma Hay Fever Urticaria and Allied Manifestations of Reaction St. Louis 1925 The C V Mosby Co

Psoriasis, which quite often disappears in pregnancy commonly recurs during lactation

The Skin in the Newborn

The skin of the normal and fully developed newborn baby is red (erythema neonatorum physiologicum) and covered with vernix caseosa The fetal lanugo hair has disappeared with the exception of some fuzz on the shoulders and on the back The head is usually covered with hair of up to one inch (2 5 cm) in length The eyebrows and eyelashes are developed The nails have a palpable horny consistency and slightly exceed the fingertips in length The panniculus adiposus is well developed and causes characteristic bulges and folds especially on the buttocks and thighs

Microscopically the horny layer of the epidermis is very thin[1765] and the nuclei stain well throughout the epidermis [1766 1767] The papillae are flat but the papillary vessels are hyperemic The tunica elastica of the blood vessels is well developed in contrast to the media and adventitia [1767] The other elastic fibers are still but little differentiated [1768] It takes about three years until the elastic reticulum is developed approximately like that of the adult The corium is rich in cells The fat cells have in contrast to the adult well discernible nuclei The Pacinian corpuscles are completely differentiated In spite of the developed musculi arrectores pilorum goose flesh does not occur in the newborn [1765] The hairs are devoid of a medulla

The sebaceous as well as the sweat glands assume their characteristic shape and full function after the fourth or fifth month[1765] of extrauterine life but secretion is present[1769] as early as the sixth month of embryonal life Milia neonatorum are either enlarged sebaceous glands or cysts filled with desquamated horn cells

The insensible perspiration is greater[1765] and the acidity of the newborn s skin is lower than in the adult The average pH of 6 7 is close to the neutral point [1770] Of course the transition from fetal to extra uterine life affects the whole system so profoundly that it is not surprising that it is recorded in the growing matrix of the nails Schick[1771] determined the rate with which the physiological nail line of the newborn moves toward the free end of the nail On the

30- 39th day the line has grown out 0 5 millimeter
40 49th day the line has grown out 1 4 millimeter
50- 59th day the line has grown out 2 3 millimeter
60- 69th day the line has grown out 3 0 millimeter
70 79th day the line has grown out 3 3 millimeter
80- 89th day the line has grown out 3 6 millimeter
90 100th day the line has grown out 4 2 millimeter

[1765] Cun tol in N P Die Beso d rh iten des Kindesalters B rlin 1921 Allg Med V lag a stalt

[1766] Tausch M Die anatomisch n Eig tümli hkeiten der N ug boren nhaut und ihre damit verbunden Disposition zu Erkrankung n Arch f Gynäk 164 376-384 1937

[1767] Chiale G D lle modificazioni dei vasi cutan i in renti all età Gior ital di dermat e sif 68 16 5 1645 1927

[1768] St ig r Kazal D Eigentümli hk iten d r Haut von Kin lern Orvosi Hetil 78 668-671 1934 Zbl 49 48

[1769] Hecht H Di Reaktionsfähigkeit d Haut beim Kin l Med Kli 32 68- 69 1936

[1770] Ta idei A Ricerche media te indi atori sulla reazione attuale d lla cute n l neonato Riv ital Ginec 18 496 519 1935

[1771] Schick B Die physiologische Nag llinie des Säuglings Jahrb f Kin l rh 67 146-160 1908

These figures were obtained from 250 measurements Heller is skeptical about the practical value of these measurements since individual variations are common

On the borderline of physiological and pathological peculiarities are the milia of the face the symphysis praeputialis which disappears by desquamation the mongol spots and the superficial epithelial cysts in the midline of the hard palate [177] Several types of flat and faintly red telangiectases are known as nevi pallidi (stork bites) Unna s nevus is a relatively inconspicuous macular purplish irregularly contoured telangiectasis of the nape of the neck Other similar vascular maculae occur on the forehead [1773] on the eyelids and elsewhere Most of these vascular nevi disappear spontaneously They should not be confused with true hemangiomas Icterus neonatorum of varying degree occurs in about two out of three babies and clears up during the first week A peculiarity of the infantile skin is its tendency to form blisters Thus scabies in early childhood syphilis and even psoriasis may produce large blebs and the urticaria of this age often shows a central vesicle and a papular appearance giving it the characteristics of strophulus The allergic skin reactions are likely to be vigorous or even violent so that a mild test reaction e g a moderately positive Pirquet should be judged with great caution [1769] Of great importance is the hemorrhagic tendency in the newborn In 66 per cent of the babies the endothelial permeability as measured by the number of petechiae elicited under controlled conditions by the application of a suction cup is increased above the adult level At the age of ten years this physiological hemorrhagic tendency has disappeared [1774]

The incidence of the more severe *hemorrhagic diathesis of the newborn* is about one in two hundred [1775] with a marked predisposition by asphyxia at birth The disease is not noticeable at birth On the third day symptoms of hemorrhagic disease such as the oozing of blood from the navel from circumcision and from other wounds or bruises may become manifest There are often large purpuric spots but according to Quick [890] petechiae are characteristically absent Melena neonatorum is the most common type of the disease This trouble is due to hypoprothrombinemia The prothrombin level at birth is near the adult level but it may fall during the first few days to as low as 10 per cent It returns to normal at the end of the first week [890] The cause of this drop is a deficiency in vitamin K The human body is unable to synthesize vitamin K which comes entirely from plants The newborn is physiologically provided with enough vitamin K from the mother to tide him over the first week until he can draw from the harvest of his intestinal flora which becomes established during this time If the baby does not get enough maternal vitamin K or if his allotment is used up or destroyed before his own is ready for use the level falls below

[1772] Mayerhofer E Hautzeichnungen der Neugeborenen Lijecn vjes 55 402-407 1933 Zbl 46 755

[1773] Hagenbuch M Ueber Teleangiektasien bei Neugeborenen Ztschr f Geburtsh u Gynäk 89 127 133 1925

[1774] Bayer W Beitrag zu den hämorrhagischen Erkrankungen des Neugeborenen Die Rolle der Endothelasthenie Jahrb f Kinderh 133 222 238 1931

[1775] Sanford H L Hemorrhagic Disease of the Newborn 358 Cases J Pediat 19 3 1931

the critical point and causes hypoprothrombinemia and hemorrhage Vitamin K restores the bleeding mechanism to normal If 2 mg of vitamin K (menadione) are given to the mother within two days before delivery the baby's vitamin K ration is increased enough to prevent hemorrhagic disease[1776] The modern treatment of hemorrhagic disease of the newborn has reduced the mortality from 57 per cent to 20 per cent[1775]

A group of phenomena in the skin of the newborn is explained by the *effect of maternal or placental hormones* *The squamous epithelium of the vagina* of newborn girls develops a marked hyperplasia and becomes piled up to a thickness of 30 40 layers with the top layer constantly desquamating[1777 1780] The vaginal smear shows an abundance of naviculated squamous cells with pyknotic nuclei indistinguishable from the smear of pregnant women This phenomenon is clinically noticeable as a creamy white discharge rarely mixed with blood from the cervix A few days after birth regression of the hyperplastic epithelium sets in and the normal infantile vaginal mucosa develops This phenomenon is so regularly found and so striking that it has been suggested to make use of it for the objective determination of the age of a newborn baby[1777]

Not as constant as the reaction of the vaginal epithelium but well known for ages is the swelling and secretion of the *mammary glands* in the newborn of both sexes (witch milk) The *linea alba* especially between the navel and mons veneris becomes pigmented in 8 per cent of the babies[1781] This pigmentation becomes visible at the age of three weeks and persists two to three months The succulence and sometimes even the swelling and fold formation of the *gums in newborns* (suckling folds) has been compared to the hypertrophic gingivitis of pregnant women[1778] (see pregnancy) The *labia majora* and also the *male genitals* of the newborn are often swollen and succulent This also may be due to hormonal influence Other influences of pregnancy have been observed in the internal genitals of male and female newborns[1779]

The comedones and the false milia i e the enlarged sebaceous glands and the sometimes observed acne of the newborn (also his vigorous lanugo growth) have often been interpreted as *hormonal pregnancy reaction* One has even in view of the numerous gonadal stimulations spoken of a miniature puberty of the newborn The hypertrichosis of the newborn has also been called a parallel to the hypertrichosis of pregnancy[1451 178]

[1775] Butt H R The Fat Soluble Vitamins Handbook of Nutrition Chicago 1943 American Medical Association

[1777] Fraenkel L and Papanicolaou G N Growth Desquamation and Involution of the Vaginal Epithelium of Fetuses and Children With a Consideration of the Related Hormonal Factors Am J Anat 62 427 1938

[1778] Phillipp E Schwangerschaftsveränderungen beim Neugeborenen Klin Wchnschr 17 797 800 1938

[1779] Neumann H O Histologische und experimentelle Untersuchungen zur Frage der Schwangerschaftsreaktion der Neugeborenen Ztschr f Geburtsh u Gynäk 99 100-136 1930

[1780] Neumann H O Schwangerschaftsreaktion im Neugeborenenorganismus Sitzungsb d Gesellsch z Beförd d ges Naturw zu Marburg 65 61 70 1931

[1781] Epstein D Über ein neues Zeichen der fetalen Schwangerschaftsreaktion Acta paediat 11 100-106 118 121 1930

[1782] Leiner C Hautkrankheiten im Säuglingsalter Handb d H u Gk 14 450-557 1930

Chapter XXV

MENOPAUSE

The known physiological changes connected with the menopause are manifold The irregularity and the final ceasing of menstruation is due to ovarian changes which may precede the actual menopause for a considerable time Failure of the formation of corpora lutea and simultaneous persistence of Graafian follicles is thought to be responsible for a temporary oversupply of estrin which may account for menopausal hemorrhage[1783] The waning function of the ovaries is followed by excessive and persistent oversecretion and excretion of the luteinizing and follicle stimulating factors of the prepituitary[1784] This amount of anterior pituitary hormone which exceeds that in pregnancy by a wide margin disappears only slowly[1785] Injection of large doses of estrogen makes the gonadotropic factor temporarily disappear from blood and urine In more than 50 per cent of the menopausal women as well as in castrates considerable quantities of the estrogenic factor circulate in the blood and are excreted in the urine[1784] Along with the hormonal changes appear a great number of symptoms nervousness exhaustion headache insomnia depression arthralgia cardiac consciousness and obesity

Dermadromes—Hot Flushes and Perspiration Formication—In the skin hot flushes and excessive perspiration are the most common physiological phenomena of the change of life In evaluations of large series of the menopausal syndrome[1783 1786 1787] the incidence of hot flushes varies from 59 to 95 per cent This is understandable since the phenomenon is extremely variable in severity In the typical fully developed spell the patient often after an abdominal aura suddenly suffers from a sensation of heat which is described as creeping from the lower parts of the body to the head The face is usually flushed In severe attacks the patient has the urge to open her dress and seek an open window in order to satisfy the sensation of air hunger After a short period of about twenty seconds to three minutes the attack ends with a profuse perspiration which often causes chills Fortunately such severe seizures are relatively infrequent and the vast majority of women experience only milder flushes The number of attacks varies from a dozen times a day for several years to a few attacks which almost pass unobserved The flushes (also called flashes) seem to be a most dependable indication of the cessation of normal ovarian function In many

[1783] Lewis T F Symposium Menopause-Disorders Rev M Progr pp 85 87 1940

[1784] Frank R T Goldberger M A and Salmon U J The Menopause Symptoms Hormonal Status and Treatment New York State J Med 36 1 9 1936

[1785] Von Haam E Laboratory Diagnosis of Menopausal and Climacteric States Rev M Progr pp 90-9 1940

[1786] Hawkinson L F Menopausal Syndrome 1 000 Consecutive Patients Treated With Estrogen J A M A 111 390-393 1938

[1787] McDowell J G and Paterson A S Physical and Psychologic Symptoms of the Menopause J Obst & Gynaec Brit Emp 47 319-3 6 1940

cases in which deep X ray therapy was directed to still functioning ovaries mostly because of pelvic malignancy the author hardly ever observed the onset of the induced menopause without flushes On the other hand if flushes failed to be noticed the sterilization was usually not accomplished Reynolds showed that the menopausal flush is caused by arteriolar dilatation He demonstrated in plethysmographic tests that the injection of estrogen in menopausal women is followed by a plateau type of vasodilatation This reaction does not cause any sensation While the plateau type response is developing a sharp increase in the tested finger volume may occur and last from three to fifteen minutes During this flush type reaction the skin temperature is elevated and the patient has a sensation of heat Excessive perspiration and formication is a complaint in about one third of the cases[1786]

Hypertrichosis —While flushes and perspiration have a physiological character a great number of dermatoses have been related to the menopause On the borderline between physiological and pathological dermadromes is



Fig [illegible] Climacteric hypertrichosis

the hair growth which sometimes appears as a more marked lanugo on the upper lip and sometimes as more or less numerous thick dark bristles on the chin and in the ears At the same time the hair on the scalp as well as the axillary and pubic hair loses much of its vigor and becomes scanty and thin In rare cases the menopausal hair growth may assume the character of a true beard which embarrasses the unfortunate woman to an extreme degree The menopausal

facial hair growth shows a remarkable similarity to the "scattered" beard of the male castrates It seems that the functioning ovary affords a certain protection against the hair growth stimulating effect of the adrenals In two cases of the literature menopausal facial hair growth was strongly stimulated by ovariectomy In one of these remarkable cases the patient had to shave twice daily and in the other the woman made the best of her condition by exhibiting herself as a bearded woman in the side show of a circus[1788] Rosenhagen tried to solve the pathogenesis of the menopausal beard by paying special attention to this question during autopsies on women above the age of thirty In thirty cases with marked beard growth the ovaries and adrenals were separated from fat weighed and histologically examined In five cases adenomas of the adrenal cortex were found but the remaining twenty five did not yield any tangible findings Perhaps the shift in the relation between the still vigorous adrenals and the atrophying ovaries suggests an explanation[1789, 1790] But if so why does not the menopausal hypertrichosis appear more frequently? Another suggested cause is the elevated prolan level in the blood and urine which together with hypertrichosis *is also found in the basophile adenoma of the anterior pituitary*

Pigmentation Benign Cutaneous Neoplasms—Changes in the pigmentation and chloasma resembling spots as well as depigmentations occur quite frequently[1791]

Stimulation of the growth of small soft cutaneous fibromas and moles is common It may be explained by the oversupply of prolan Similar phenomena can be observed in pregnant women The so called cutaneous tags or small fibromata pendula around the neck are very common in menopausal and especially obese women

Obesity—The panniculus adiposus is very often increased Careful study of the blood chemistry basal metabolism etc has so far failed to find the cause[1784] Some women become thinner with the change of life

Pruritus Vulvae Leukoplakia Kraurosis—Pruritus vulvae is common in the menopause There are many causes or combinations of causes which may lead to pruritus and its related conditions The most common irritations those caused by discharge and infected urine[1792] do not strictly fall into the scope of this book Oxyuriasis does not seem to play a major role in *vulvar pruritus of the menopause but mycotic infection* is very common in America in contrast to Europe

Latent diabetes with or without sugar in the urine often causes pruritus vulvae[1793] Coincidence with the menopausal age may often cause the physician

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[1788] Kovacs F Beitrag zur Pathologie des Hirsutismus und Virilismus Monatschr f Geburtsh u Gynäk 91 65-79 1932

[1789] Eberling r W Klimakterische Gesichtsbehaarung und endokrine Drüsen Ztschr f d ges Anat Abt 2 Ztschr f Konstitutionsl 10 412-433 1924

[1790] Eberling r W B Zur Frage der Gesichtsbehaarung bei Frauen Ztschr f d ges Anat Abt 2 Ztschr f Konstitutionsl 12 193 214 1926

[1791] Naegeli and Keller M Haut und Klimakterium Endokrinologie 8 81 121 1931

[1792] Hall A Treatment Pruritus Vulvae Brit J Dermat 52 3 1 338 1940

[1793] Win L H and Strakosch F A Vulvar Pruritus as Possible Early Symptom of Unrecognized Diabetes Journal Lancet 60 532-534 1940

to treat such patients with hormones instead of applying more sensitive tests for detecting diabetes It seems as though the part which the various etiologic factors have been accused of playing depends on the various authors Still after the deduction of all the readily explainable cases of pruritus vulvae there remains a group which can be linked to hormonal disorders as was suggested a long time ago [1794, 1795] mainly because of coincidence with menstruation hypomenorrhea[1796] and particularly the menopause and castration [1794, 1797, 1798]



Fig 23 Kraurosis vulva

Lately based on blood assays unexpectedly high estrogen values in the menopause have been *found together with pruritic conditions of the vulva* [1799] *The frequent* reports of successful treatment with estrogens have done much to establish the general opinion of a hormonal etiology

It has been attempted to separate chronic pruritus vulvae leukoplakia and kraurosis Since transitional pictures are common and the same case may in its course pass through all the varieties it is justifiable to deal with them

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[1794] Brocq L Kraurosis Bull Soc franç de dermat et syph 1912 also Ann de dermat et syph Abstr Dermat Wchnschr 62 308 1916

[1795] Taussig F Precancerous Lesions of the Skin of the Vulva Leukoplakic Vulvitis Kraurosis Pruritus Arch Dermat & Syph 1 621-635 1920

[1796] Ferrari A B Presentazione di un caso clinico Gior ital di dermat 68 1466-1467 1927

[1797] Lathardt A Pruritus Vulvae Etiology and Therapy Schweiz med Wchnschr 70: 121 1214 1940

[1798] Terruhn E Kraurosis Vulvae Arch f Gynäk 134 578 1928

[1799] Shute F Degenerative Vulvovaginitis Associated With Estrogen Imbalance J Obst & Gynaec Brit Emp 49 482-498 1942

together The disease starts with a subacute dermatitis of the vulva and often of the perianal area There are exacerbations with oozing and widening of the involved area followed by regressions Secondary infection especially folliculitis and irritation from scratching is common A certain percentage of the cases may heal in this stage while others may develop a condition which is quite different from chronic eczema The skin which was red and succulent before gradually acquires a leathery rigid character and cracks easily It becomes more and more depigmented pearly or bluish white and dry The hair the labia minora and the clitoris disappear Finally atrophy of the vulva with white thin skin develops The introitus vaginae may become contracted Pruritus is present in all stages and on close inspection leukoplakia can be found in almost every instance[1795] It is from these leukoplakic patches that cancer develops in more than fifty per cent of the cases The histologic picture corresponds to the described clinical sequence Hyperkeratosis acanthosis and inflammatory infiltration of the upper derma is followed by thinning of the epidermis and loss of pigment and elastic fibers The papillae disappear completely Many patients with chronic vulvar eczema never develop leukoplakia and kraurosis and cancer is rare in these nonleukoplakic cases

Treatment of the pruritus vulvae based on the elimination of the mentioned etiologic factors is not often possible Besides various local procedures estrogen therapy should be tried The dosage advised has become higher and higher Foss[1800] starts the treatment with injections of from 10 to 25 mg of estradiol benzoate twice weekly As improvement occurs the injections are reduced to one a week Smaller doses are necessary if local treatment in the form of ointment containing estrone estradiol or estradiol benzoate is used Foss gives the following formula for the ointment

Estradiol benzoate consisting of	10 milligrams in sesame oil mixed with 100 grams of a base	
	Halibut liver oil	20 parts
	Cerae albae	16 parts
	Adipis lanae	2 parts
	Sodium biborate	1 part
	Ol amygdalae	41 parts
	Aquae	20 parts

A great number of similar creams have been advised[1801 1803] The massaging into the thoroughly cleansed skin of 0 5 mg of estradiol in sesame oil seems a practical method[1804] This should be done once daily by the physician Later the patient may follow it up with an estrogen cream

[1800] Foss G L Further Developments in Treatment (Pruritus Vulvae) J Obst & Gynaec Brit Emp 46 771 88 1939

[1801] Klaften F Treatment of Essential Pruritus and Kraurosis Vulvae by Simultaneous Local and Parenteral Administration of Estrogen J Clin Endocrinol 3 218 23 1943

[1802] Lubowe I I Stilbestrol (Estrogen) Cream in Pruritus Urol & Cutan Rev 45 314-315 1941

[1803] Schrattenbach A Oestroglandol (Estrogenic Preparation) in Therapy of Pruritus Vulvae Wein med Wchnschr 88 908 909 1938

[1804] Kerr rkian A Treatment of Chronic Pruritus With Local Applications of Estrogen New England J Med 220 661-663 1939

Suppositories containing 0 36 mg of di hydro oxygestrin in 2 grams of cocoa butter have been found effective when inserted into the vagina once or twice daily

It seems as if the initial enthusiasm about the hormone therapy of vulvar pruritus is subsiding [1800, 1805, 1806] It is certain that estrogen therapy not infrequently fails The difficulty of finding out the suitable cases has led to the unsuccessful treatment of many cases It is furthermore agreed that only few patients achieve complete and lasting comfort Relapses which require further local therapy or a few injections are common The more severe cases need almost continuous substitution therapy in one form or another [1800] Some authors are reluctant to administer the estrogen locally over a long time because of the danger of producing cancer in a condition which is precancerous in itself Finally adverse effects like uterine bleeding in menopausal women and local exacerbations are known to occur However the fact remains that estrogenic therapy in many cases is one of the best methods we have for giving relief in a very annoying condition

Similarly as in neurodermitis to which pruritus vulvae has other parallels the gastric hydrochloric acid has been found low or completely lacking in about one out of three cases The more severe cases of kraurosis and leukoplakia are associated with achlorhydria [1800, 1807] These cases seem to be benefited by regular HCl medication Vitamin A in any convenient form[1800] and vitamin E or wheat germ oil in very high doses[1799] as well as vitamin B_2[1808, 1809] and uncooked diet have been recommended but not enough convincing experience has been forthcoming

In discussing the internal therapy of the pruritic conditions of the vulva the importance of the various local methods such as antipruritic salves and lotions surgical procedures and radiation therapy should not be forgotten

Miscellaneous —The great number of cases of eczema herpetiform eruptions pruritic attacks and other dermatoses which have been labeled as menopausal because they appeared in women at the age of forty to fifty five have rarely been investigated closely enough to corroborate this claim Naegeli and Fellner[1791] believe in a higher cutaneous sensitivity in the menopause just as is present during menstruation This is supposed to account for many of the eczemas in middle aged women High urinary prolan does not prove more than the onset of the menopause and therefore does not confirm gonadal origin of the dermatosis in question The best though still not a perfect proof is prompt cure after treatment with estrogen [1810]

[1805] ...sa ill A Pruritus Vulvae Leukoplakia and Kraurosis J Obst & Gynaec Brit Emp 49 310-327 194

[1806] R is R Pruritus Leukoplakia and Kraurosis in Patient Aged 6? 8 Clin North America 20 10? 116 1940

[1807] Swift B H Achlorhydria and Pruritus Vulvae J Obst & Gynaec Brit Emp 43 10 3 1936

[1808] Kunez D Pruritus Vulvae Vitamin A and Vitamin B_2—Complex in Therapy Zbl f Gynäk 66 9?? 9?7 194

[1809] Fymer H Pruritus vulvae Deutsch med Wchnschr 68 961 96 1942

[1810] Leszczynski R and Lubha s 8 Dermatose bei Frau on a f hormonal r Grundlage Przegl dermat 26 ?13 2 9 1931 Zbl 41 ?0 193?

A tendency to *edema* in various forms is an often mentioned climacteric manifestation There are slight fugitive edemas of the extremities and also of the face which develop over night and disappear during day time[1815] Angioneurotic edema (Quincke s edema) is undoubtedly more common in the menopause and may then respond to hormonal therapy

Urticaria factitia and an urticarial character of various types of dermatitis is often mentioned in connection with the menopause



Fig 1 Fig 2

Figs 1 22 Keratoderma climactericum (Haxthausen) Discrete palmar hyperkeratoses fissuring ab n of eel les frequently with obesity and hypertension following menopause (Courtesy Dr H Haxthausen Copenhagen Denmark)

Haxthausen[1815a] described as *keratoderma climactericum* ten cases of a dermatosis which he observed in women who besides the symptoms of menopause showed some degree of obesity a normal basal metabolism arterial hypertension and occasionally arthritis

In the early stages the skin changes consist of lentil size discrete scaly keratoses apparently without inflammation They are seen on symmetric spots of the palms and soles Later they can hardly be differentiated from eczema

[1815] Curschmann H Ueber klimakterisches Oedem Med Klin 28 1 0-1 71 1933
[1815a] Haxthausen H Keratoderma Climactericum Brit J Dermat 46 161 1934

The relative frequency of *pemphigus* in the menopause has been emphasized[1812] The author is inclined to confirm this impression

Rosacea and telangiectases are often mentioned in connection with the menopause The same applies to Fox Fordyce disease to Poikiloderma atrophicans vasculare calcifications of the skin acrodermatitis atrophicans Raynaud s syndrome scleroderma erythema perstans trophedema[1813 1816] xanthelasma and other dermatoses

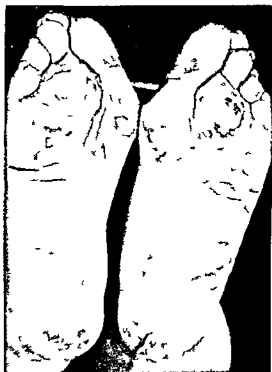


Fig 6 I ratoderma clima t ricum (Haxthausen) (From Lynch F W Ar I D rmat & Syph 1943)

[1812] Werth r J P mphigus Arch f Dermat u Syph **151** 179 1926

[1813] Milroy F W An Und scrib d Variety of Hereditary E1 ma New York M J **56** 505 1892

[1814] Milroy F W Ch onic Hereditary Edema J A M A **91** 117 19 8

[1815] Chvost k F Xanth la ma u d Ikterus Ztschr f klin Med **73** 479 1911 W1 n klin Wchnschr **22** 1630-163 1910

[1816] Adlersberg D Beoba htung n bei in r au gedehuten Xanthomatose Arch f D rmat u Syph **148** 300 19

Chapter XXVI

MISCELLANEOUS DERMATOSES WITH ENDOCRINE BACKGROUND

Dermatitis Dysmenorrheica Symmetrica —In 1912 Matzenauer and Polland[1817] published six cases of an unusual dermatitis in dysmenorrheic mostly young, girls The attacks or crops were not in connection with the menses The lesions appeared in patches which were mostly round on the trunk and more oblong on the extremities They were approximately symmetrical except in or close to the midline The individual lesion started with a burning sensation followed by a pale red urticarial erythema the tinge of which was different from the early stage of ordinary dermatitis Within half an hour the urticarial infiltration made the follicles stand out Serum exuded into the follicles and formed a thin yellowish crust on the follicular orifice These follicular lesions often coalesced within a few hours to form large weeping or crusty patches which were still slightly elevated because of their urticarial component and surrounded by a narrow inflammatory margin Follicular extravasations often gave the patch a characteristic dotted appearance The varying intensity of the changes could produce all degrees of inflammation running the gamut of exudative and hemorrhagic stages to the severe destruction of connective tissue with scar formation The lesions healed quickly within a few days unless deeper destruction occurred which was rare In these cases the picture and course was that of a dry necrosis and slow demarkation caused by an anemic infarct The patches appeared most often on the face and less often on the hands arms legs and upper trunk In one case the oral and laryngeal mucosa was involved

Looking at the pictures of the original article one cannot help thinking of artifacts produced by striking or rubbing the skin with the fingers The authors were fully aware of this impression and did everything imaginable to rule out self inflicted lesions[1818] They observed some patches developing while the patient was asleep or under impervious dressings of zinc gelatin The buccal and laryngeal lesions certainly could not be self inflicted When a lesion was observed to appear on one leg the corresponding spot of the other leg was immediately covered by a zinc gelatine dressing When this dressing was removed after two hours of constant medical watching a typical patch was found It was impossible to produce typical lesions by mechanical and electrical irritation by spraying with ethyl chloride or by other methods

All patients were suffering from *dysmenorrhea* The menses were irregular connected with many complaints and the flow scanty Puberty and the onset

[1817] Matzenauer R and Polland R Dermatitis Symmetrica Dysmenorrhoica Arch f Dermat u Syph 111 385 1912

[1818] Polland R Neue Beiträge zur Klinik der Dermatosis dysmenorrhoica Arch f Dermat u Syph 121 453-460 1921

small patch hidden under the hair to the size of a whole leg The spots are often found on the nape of the neck on the lower back and on the buttocks They resemble the milk coffee spots seen in von Recklinghausen s neurofibromatosis These areas of pigmentation indicate some relationship to the skeletal involvement Unilateral bone disease is usually accompanied by ipsilateral pigmentations widespread bone lesions by numerous and large pigmentations

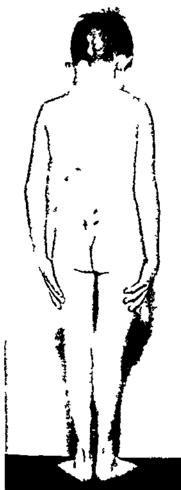


Fig 23 —Albright s yndrom Note areas of pigmentation (Court y Wis onsin General Hospital)

The blood calciu ... d ... normal this is important in the differentiation of hy ... of at least twenty five recorded exp ... never been found The differ ential ... is ... osis H ... Christian s xanth ... omas ... and some other ... s ... disease pig

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[1817] Matzenauer R and Polland R Dermatiti Symmetrica Dysmenorrhoica Arch f Dermat u Syph. 111 385 1912

[1818] Polland R Neue B iträg ur Klinik de D rmatosis dysm norrhoica Arch f Dermat u Syph. 131 453-460 1921

of menstruation had often been late in one case precocious Psychopathic stigmata and functional circulatory disorders were noted

There is no doubt that the syndrome described by Matzenauer and Polland is an unusual one It must be very rare and the geographic distribution very uneven While the six original and two of the later cases of the conspicuous dermatosis were seen in the clinic in Graz Austria almost all the other cases so far about forty were seen in European and American centers which handle great numbers of patients Only part of the forty cases published so far closely resemble the original description[181 18 3] The classical clinical picture of round oblong or fingershaped symmetrical patches does not seem to be a requirement anymore since cases of various types of dermatitis associated with ovarian dis orders have been published as dermatitis dysmenorrheica This has apparently been done with the consent of Polland who in 1935 in an abstract written by him did not object to Urbach s[1470 18 4] including some cases of erythroderma and neurodermatitis into the syndrome called Dermatitis dysmenorrheica

This depreciation of the morphology has come about by the progress achieved in determining the etiology of the menstrual dermatoses Urbach believes that the reactivity of the individual determines the morphology of menstrual derma toses of a given dyshormonal causation Thus today the term dermatitis dys menorrheica includes various dermatoses associated with menstrual disorders

Urbach and Kitamura[18 4] in their case of menstrual neurodermatitis labeled as dermatitis dysmenorrheica found the urinary excretion of gonadotropic substances increased while the estrogen content of the urine appeared to be lower than normal The patient was improved by estrogens and progesterone also by bleeding and laxatives The effect of the latter kind of treatment suggests a toxic factor According to Urbach it is occasionally possible to demonstrate that in dermatitis dysmenorrheica the premenstrual blood contains a substance which when injected into the skin of the patient during the intermenstruum will evoke an immediate urticarial reaction and a delayed response in the form of pinpoint sized papules clinically resembling the menstrual dermatosis Such a reaction could not be elicited in the patient with her own intermenstrual serum or with premenstrual serum from normal women Normal control persons did not respond to the premenstrual serum of the patient Probably as in the other menstrual dermatoses allergic as well as toxic and possibly neuro psycho genic factors may be of importance Pregnancy and cessation of the menses

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Friedberg J Dermatitis symmetrica dysmenorrhoica Arch f Dermat u Syph 111 173 184 1912

[1] Wise F and Lakhurst So-Called Dermatitis Dysmenorrhoica Arch Derm & Syph 2 723 19 0

[1921]Wirz F Gibt es ein spezifisch dysmenorrhoische Hautkrankung Arch f Dermat u Syph 136 36-47 1921

[1 3]Hauck I Beitrag zur Dermatosis symmetrica dysmenorrhoica (Matzenauer Polland) Wien med Wchnschr 75 316-318 4 0-453 19

[1 4]Linden r I Uber die sog Dermatitis symmetrica dysmenorrhoica Diss F lang u 19 Zbl 10 006

[1 4]Urbach F and Kitamura S Uber pathologisch Ausscheidung von Sexualhormonen bei einem Fall von Dermatitis dysmenorrhoica (Polland Matzenau) Klin Wchnschr 11: 271 274 1935

prevents the attacks This has been demonstrated in several instances when after failure of other measures X ray castration was resorted to [1470 1925]

In several cases monthly attacks preceded the unusually late menarche and failed to appear later [18 6-18 8] In two cases of symmetric dermatitis dysmenorrheica marked prolanuria could be demonstrated [14 5]

The treatment should tend to correct any endocrine disorder If this fails the desensitization with premenstrual blood after the methods of Geber and Lehner and Rajka should be tried (see menstruation) Estrogen salve (5000 units per gram of Aquaphor) has been claimed to be successful locally [1829] Castration must be reserved for severe and intractable cases

Fox-Fordyce Disease —The dermatosis in question is a chronic symmetrical papular itching eruption involving the armpits and the pubic area The axillary lesions form a diamond shaped palm sized group of closely set yet discrete firm shotty perioral papules of pinhead to pea size The papules are of normal or pink color only little excoriated and mostly arranged in beaded rows which cross the axilla These grater like rows can be well demonstrated by stretching the skin This dermatosis is with rare exceptions extremely itchy so that the axillary hair is usually rubbed off Similar lesions occur though much less often in the pubic area and in the skin of the external genitalia and the navel [1830]

The pathologic changes consist of acanthosis parakeratosis keratosis and inflammation mainly surrounding the openings and lining the ducts of the apocrine sweat glands and of the hair follicles The orifices of the involved glands are usually blocked by a keratotic plug

The disease is quite rare and seems to affect pigmented races more often e g the Negroes and Jews (Jadassohn in discussion[1831]) Only in a few (4) instances has it been observed in the male [183 1833] The eruption is almost exclusively a disease of the menarche It has never been seen before puberty at which period it sometimes starts [1834] The menopause may bring the trouble to an end[1835] but the disease may also be provoked at this time [1836] The dis-

[18] Berde I Fall von To l oderma m truale mit erysip loidartigen Erscheinungen Gyn at betil 68 201 203 1923 Zbl 15 435

[1 26]Tragant J Die dysmonorrhoische symmetri che De matitis (Pollandsche krankbei) Rev méd. de Barc lona 4 538 19 5 Zbl 20 60 19 6

[1 27]Tragant J Die symmetrische dysm norrhoische N krose Crón méd mexicana 25 11-1 19 6 Zbl 22 304 19 7

[1 28]Artom M Consid ra io i cliniche ed e io-patogenetich intorno all dermatosi simmetriche di me or oich Arch ital di de mat u sif 6 513 550 1931

[1 2] R iff rachei l W Zur B handlung ovariell bedingter Dermatos n mit Follikelhormon München med Wchnschr 81 1700 1937

[1830] Al xand A Fox Fordyce sche Krankheit Handb d. H u Gk 8 1 433-445 19–

[183] Pick W Zur Pathogenese d r Fox Fordyce hen Krankheit Arch f Dermat u Syph. 111 165 19 6

[1832]Kaufman S M Fox Fordyce s Dis as in M le New York State J Med 28 9 1473 1928

[1833]Steig r l azal D Fo For lyce-Erkrankung Zbl 35 454 1930

[183] Tappeln r S Fo Fordyce Dis ase Arch. f Dermat u Syph. 176 59-60 1937

[1835]Gori München med Wchnschr 79 533 1932

[1836]Dowli g G B and F man L Fo Fordyce Di ase Proc Roy Soc Med 25 1031 1032 1932



Fig. 227



Fig. 228

Figs. 227, 228. Fox-Fordyce disease (Courtesy Dr. Frank Vero, Vanderbilt Clinic, New York)

order seems to improve in pregnancy [1481, 1837] Ovarian deficiency with amenorrhea dysmenorrhea infantilism, cystic ovary and other sexual dysfunctions have been described in the great majority of cases [1, 31, 1838, 184] Premenstrual and menstrual exacerbations which may climax in violent pruritic spells is often mentioned Hyperthyroidism[1843] and hypothyroidism[1841] have been found much less often than ovarian deficiency



Fig 3 – Fox Fordyce d a e Extrem ly itchy sut id t un l r x ray treatm t

Considering the well known sexual relationship of the apocrine glands (see Puberty) and the evidence of accompanying ovarian disorders an ovarian etiology seems very probable This is further supported by the response to estrogen therapy and in some cases proluton therapy [14 0, 1844, 1846] Some authors believe that the condition is not curable and others think that roentgen therapy is the most effective treatment

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[1837] Gougerot and Blum P Maladi de Fox Fordyce non pru it in use Bull Soc franç de dermat et syph 39 700-701 1932

[1838] Lortat-Jakob and Gastinel L n a de maladi d Fox Fordyce Bull Soc franç de dermat t syph 36 1? 1939

[1839] Kemeri D Fox Fordy esch krankheit Zbl 29 13 1931

[1840] B inbau r Fo Fordyce Disease Arch Dermat & Syph 12 572 19 5

[1841] Goodman M H an I Soloman M Fox Fordyc Di as Estrogenic Studies) Arch Dermat & Syph 29 907 1939

[1842] S z p J Hormo al Dysfun tion in Fox Fo dy Di ea Orvos hetil 83 56-59 1939 Abstr D rmat Ztschr 77 124 1 1938

[1843] Neumark S La mal di de Fox Fordyce Ann I d mat t syph 8 999 1931

[1844] Brandt F Corpus Lut um Hormon Th rapy (Pruritu Vul ae) München med Wchnschr 87 42-43 1940

[1845] Ro burgh A C A Case of Fo Fordy Di ease B it J D rm 55 121 1943

[1846] Kertesz C S Hormones in Th rapy f Fox Fo dyce Disease Dermat Wchnschr 112 733 736 1941

Albright's Syndrome.—This typical combination was first recognized by Fuller Albright[1847] who described a triad of disseminated osteitis fibrosa, areas of cutaneous pigmentation which have a distribution suggesting some connec-



Fig. 30.—Albright's syndrome. Areas of pigmentation and precocious puberty. (From Albright, F., Butler, A. M., Hampton, A. O., and Smith, P.: New England J. Med.)

tion between them and the bone lesions, and sexual and somatic precocity when the disease occurs in the female sex. Pathological fractures are common.

[1847] Albright, F., Butler, A. M., Hampton, A. O., and Smith, P.: Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction With Precocious Puberty in Females, New England J. Med. 216: 7 40, 1937.

According to Lichtenstein and Jaffe[1848] who reviewed ninety cases, among them fifteen of their own, the syndrome is not extremely rare if one includes the incomplete cases. The disease affects girls more often than boys, the ratio being about 3:2. The first symptom is often a pathological fracture which leads to x-ray examination of the bones. Scattered but often unilateral patchy cystlike lesions of osteitis fibrosa are found. There are always parts of the skeleton showing normal bones.[1849, 1850]



Fig. 31. Albright's syndrome. Osteitis fibrosa disseminata. (From Albright, F.: New England J. Med.)

In the female, sexual precocity with early onset of menstruation and development of secondary sex characteristics and early bone age occurs in about one third of the cases.[1] The sexual development in the male patients is normal. In the skin there are smooth, brown, nevus-like patches of oblong, round or jagged shape. They vary in size from a group of freckle-like spots or a single

[illegible] Dysplasia of Bone Condition Affecting One [illegible] mal Pigmentation of Skin Premature [illegible] 33 [illegible] 16 194[illegible]
[illegible] Differential Diagnosis of Hyperparathyroidism With Especial Reference to Albright's [illegible] New York State J. M. [illegible] 43 [illegible] 1943
[illegible] Campbell [illegible] Da [illegible] and Rust [illegible] Albright syndrome [illegible] 35 3 [illegible]

small patch hidden under the hair to the size of a whole leg *The spots are often* found on the nape of the neck on the lower back and on the buttocks They resemble the milk coffee spots seen in von Recklinghausen s neurofibromatosis These areas of pigmentation indicate some relationship to the skeletal involvement Unilateral bone disease is usually accompanied by ipsilateral pigmentations *widespread bone lesions by* numerous and *large* pigmentations

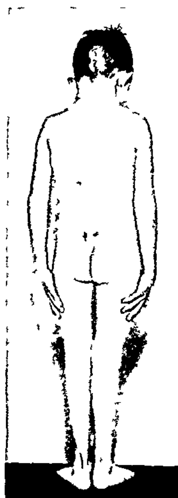


Fig 23 Albright syndrome Note areas of pigmentation (Courtesy [illegible] General Hospital)

The blood calcium and blood phosphorus are normal this is important in the differentiation of hyperparathyroidism In spite of at least twenty five recorded explorative operations a parathyroid tumor has never been found The differential diagnosis has to rule out neurofibromatosis *Hand Schüller Christian s* xanthomatosis Paget s disease multiple hemangiomas of the bones and some other rare conditions The diagnosis is easy if the classic triad of bone disease pig

mentation and precocity in the female is present Several patients started life with icterus gravis neonatorum which persisted for months [1851, 185]

The etiology is unknown An embryonic defect (Albright) seems likely The twin brother of one patient was normal In some cases a positive Babinski suggests a participation of the nervous system [1853]

The prognosis of the disease should be guarded but not too pessimistic In one case precocious puberty was followed by normal adult sex life with the consequent production of a healthy child The bone disease may become arrested The individual bone lesion is amenable to surgical treatment

It is of interest that Lena Medina of Peru who gave birth to a child at the age of five probably represented such a case of Albright s syndrome Her attending physician Dr Gerardo Lozada of Pisco Peru informed Dr Albright that she had both the brown spots and bone changes together with the precocity

Geroderma Genito-Dystrophicum Progeria —In this rare syndrome which has been seen starting early in life in both sexes the most striking feature is the senile appearance of the skin and particularly of the face There are many fine wrinkles, the skin is flaccid yellowish and the subcutaneous fat and the muscles on the distal parts of the extremities are usually extremely reduced The hair is either completely lacking or restricted to the scalp The skin gives a senile atrophic impression which make children or relatively young persons look old Diffuse and early arteriosclerosis is a characteristic feature Generalized pigmentation has been seen The nails are thin and brittle The skeleton is either eunuchoid or dwarfed The intelligence is intact Many endocrine symptoms like diabetes insipidus exophthalmos polyphagia and amenorrhea have been described The testicles are atrophic Aplasia or atrophy of the thyroid and tumor or sclerosis of the pituitary have been found at autopsy The disorder is probably related to Simmond s disease in which precocious senility is also a feature [1854] In spite of the severe changes the mentality remains alert and the patients may live for many years [1855, 1856] A syndrome of infantilism with web formation of the skin along the neck is known as *Turner s*[1857] *syndrome* In one autopsy case[1858] no functioning ovarian tissue could be found There was no axillary hair present and the pubic hair was scanty

Scleroderma Poikiloderma, Acrodermatitis Atrophicans —The voluminous literature on these rare dermatoses is replete of reports on accompany

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[1851] Brailsford J F Osseous Dystrophy Following Icterus Gravis Neonatorum Arch Dis Childhood 14 181 202 1939

[1852] Sommerfeldt P and Brown A Osteodystrophia fibrosa Am J Dis Child 57 90 101 1939

[1853] Dockerty M B Meyerding H W and Wallace G T Albright s Syndrome Proc Staff Meet Mayo Clinic 19 81 88 1944

[1854] Curschmann H Die Simmondssche Krankheit Med Klin. 32 895-897 1936

[1855] Marinesco G and Parhon C I Su un cas de diabète insipide avec cachexie hypophysaire infantilisme sénilisme atrophie des organes génitaux et convulsions de type épileptique Rev franç d endocri ol 10 105 146 193

[1856] Thannhauser S J Werner s Syndrome (Progeria of the Adult) and Rothmund s Syndrome Ann Int Med 23 559-626 1945

[1857] Turner H H A Syndrome of Infantilism Congenital Webbed Neck and Cubitus Valgus Endocrinology 23 66-574 1938

[1858] Sharpey-Schafer E P Pterygonuchal Infantilism (Turner s Syndrome) With Postmortem Findings Lancet 2 559-560 1941

ing and often contradictory endocrine symptoms although no definite relation ship has evolved In *scleroderma* the most frequently observed and best founded systemic relationship is a disturbance of the *calcium* metabolism Thibierge and Weissenbach[1859] demonstrated calcium deposits in the sclerodermatic skin Later this observation was often confirmed [1860 1861] but its significance denied again more recently [186] The blood calcium and also the phosphorus were often found to be above normal [1863 1866] and the tolerance to calcium, expressed by the ability to restore the normal calcium level in the blood after injection of calcium was found disturbed [1867] Both calcium and phosphorus are retained in the body in scleroderma[1866] which is not in line with the negative calcium balance in hyperparathyroidism to which the relation seemed suggestive [1868] The Hamilton Schwartz test for parathyroid hormone showed high values in the circulating blood in two out of three cases of so called *Werner s syndrome* (adult progeria) This syndrome is a rare heredo familial disease in which scleroderma blue sclerae hypogonadism trophic ulcers metastatic calcification osteofibrosis and other endocrine stigmata are the main features [1858 1869] The Hamilton Schwartz test was negative in two ordinary cases of scleroderma [1870] There is some evidence in support of hypoparathyroidism in scleroderma[1871] in the rare cases of its association with tetany

Primary atrophic and absorptive changes[187 1873] prior to the scleroderma in the *phalanges* and in the distal ends of other bones [1874] *osteomalacia* [1875 18 6]

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[1] Thibierge and Weis enbach Concrétions calcaires sous-cutanées et clérodermie Ann de lermat et syph p 1 9 1911

[1860] Kennedy R L J Calcino is and Scleroderma Treatment by Ketogenic Di t J Pediat 2 667-673 193

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[186] Hillmann H Beitrag zur Kenntnis der Sklerodermie Diss Hamburg 1930

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[186] Cornbleet T and St uck H C Calcium Metaboli m in Scl rod rma Arch D rmat & Syph 35 188 1937

[1867] Rothma S and Weiss I Calciumbela tung prob n b i Sklerodermie Klin Wchnsch 10 1 85-1586 1931

[1868] Burch G E Sclerod rma Sympo ium New Orleans M & S J 92 1 21 193

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[187] Win r N H Th Hamilton S hwartz Test and Hyp rparathyroidism in Va i us Di a es Am J M S 202 61 -630 1941

[187] Mamon H S l'rod rmi t parathy oi les Gaz d hôp 105 375 19 9

[1872] Bársony T and F isch F Beiträg zur Röntg ol gi I r Akroski rose Fortschr a d G b d Röntg nstrahl n 47 287 293 1933

[1873] Le ich R and Jung A Nature t origine d la sclérodermi Bull Soc franc de dermat et syph 42 6 -69 1935

[187] Lebon J M n eau Fal regoul and Georges Un cas de sclérod rmi avec gros troubles de l ossifi ation Rôl des parathyroides Bull et mém Soc méd d Hôp le Paris 53 921 0 9 1937

[1874] Morawiecka J In as d maladie de Basedow associée à la sclérc l rmi et à l ost om lacie R v neurol 2 717 7 19 8

[1875] St rling W De Ilpoly trophischi e und ler osteomala ische Typus d r S lto-skl roderma tischen Deg n ration l ol ka ga I k 7 99-103 19 8 Zbl 27 151

bilateral cataract[1856 1877 1879] the experimental production of scleroderma like skin changes in young rats and pigs following injection of parathormone[1880 1881] and finally the relatively successful *treatment of scleroderma* by unilateral *parathyroidectomy*[186 188 1884] have given support to a *hyperparathyroid* etiology, especially since some of the excised parathyroids were found hypertrophied or inflamed[1885] However the results of parathyroidectomy are still controversial[1868]

There are many observations suggesting *other endocrine dysfunctions* Amenorrhea dysmenorrhea[1889 1886 1888] onset of the disease in pregnancy and in the spontaneous and induced menopause[1 30 1889 189] findings of ovarian changes the therapeutic success of estrogens,[1893 1895] and the 3 1 predominance of the female sex[1896] are reasons enough to consider the *gonads* The situation is similar with regard to the pancreas thyroid[1897] and pituitary It is now generally accepted that *acrosclerosis*[1898] or sclerodactylia is essentially different from the diffuse or localized scleroderma (morphea) According to Sellei[1880] *acrosclerosis is a vegetative neurosis* and is related to Raynaud s disease True *scleroderma* however seems more likely to be a *fermentative* disorder related to the *pancreas* It has in some instances been successfully treated with pancreas liver stomach and duodenum extracts (Sellei[1880] and many other articles by the same author)

[1877] Krebs E Hartmann E and Thibaut F Un cas familial de syndrome de sclérodermie avec cataracte troubles endocrinens et neuro-végétatifs associés Rev neurol 1 606-618 1930 Zbl 36 21

[1878] Sézary A Favory A and Mamou H Syndrome tardif de sclérodermie avec cataracte associé à des troubles endocriniens Bull et mém Soc méd Hôp de Paris 46 3,8 1930

[187] Eguchi H Cataract bei pluriglandulärem Infantilismus mit Sklerodermie Acta Soc ophthal Jap 35 167 1931 Zbl 38 6 5

[188] Sellei J Scleroderma verum und Akroskl rose Verh 9 internat Kongr Dermat 1 ~ 8 1935 Zbl 53 98 1936

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[1884] Basch G R Leibovici R Durupt A and Bach M Sclérodermie avec concrétions calcaires (syndrome de Thibierge-Weissenbach) associée à une atrophie cutanée Parathyroidectomie Bull et mém de hôp de Paris 50 516-5 1 1934

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[186] Livierratos S G and Tsellos I A Ein Fall von universeller Sklerodermie Wien klin Wchnschr 45 1410 144 193

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[1] Schoenhof Sklerodermie Zbl 23 61?

[1] Linser K Sklerodermie Zbl 31 657

[1893] Harvier P and Lichtwitz A Sklerodermie Zbl 30 2 19

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[97] Rothman S Endokrine Störungen bei Sklerodermie Klin Wchnschr 4 1691 19

[1] Sellei J Sklerodaktylie progressive Sklerodermie (Akrosklerose) Dermat Ztschr 61 138 146 193

ing and often contradictory endocrine symptoms although no definite relationship has evolved. In *scleroderma* the most frequently observed and best founded systemic relationship is a *disturbance of the calcium metabolism*. Thibierge and Weissenbach[184] demonstrated calcium deposits in the sclerodermatic skin. Later this observation was often confirmed[185-186] but its significance denied again more recently.[187] The blood calcium and also the phosphorus were often found to be above normal[188-189] and the tolerance to calcium expressed by the ability to restore the normal calcium level in the blood after injection of calcium was found disturbed.[190] Both calcium and phosphorus are retained in the body in scleroderma[190a] which is not in line with the negative calcium balance in hyperparathyroidism to which the relation seemed suggestive.[191] The Hamilton-Schwartz test for parathyroid hormone showed high values in the circulating blood in two out of three cases of so-called *Werner's syndrome* (adult progeria). This *syndrome is a rare heredofamilial disease* in which scleroderma, blue sclerae, hypogonadism, trophic ulcers, metastatic calcification, osteofibrosis and other endocrine stigmata are the main features.[192-193] The Hamilton-Schwartz test was negative in two ordinary cases of scleroderma.[193] There is some evidence in support of hypoparathyroidism in scleroderma[194] in the rare cases of its association with tetany.

Primary atrophic and absorptive changes[195-197] prior to the scleroderma in the *phalanges* and in the distal ends of other bones[198] or *acrosclerosis*[199-201]

[184] Thibierge and Weissenbach: Concrétions calcaires sous-cutanées et sclérodermie. Ann. de Dermat. et Syph. [illegible] 1911.

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[191] [illegible] and [illegible]: [illegible] bei Sklerodermie. Klin. Wchnschr. 10: [illegible] 1931.

[192] [illegible]: Scleroderma syndrome. New Orleans M. & S. J. 92: [illegible] 1939.

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[194] [illegible]: Beitrag zur [illegible] der Skleroklerose. Fortschr. a. d. [illegible] 47: [illegible] 1933.

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[195] [illegible] J., [illegible] and [illegible]: Un cas de sclérodermie avec gros troubles de [illegible] parathyroïdes. Bull. et mém. Soc. méd. d. hôp. de Paris 48: [illegible] 1932.

[illegible]: [illegible] associée à la sclérodermie et à l'ostéomalacie [illegible] 1928.

[196] [illegible]: [illegible] osteomalacische Typus der [illegible] sklerodermie [illegible] 103 [illegible] 27: 151.

Among the many endocrine symptoms which have been reported in connection with the rare *poikiloderma atrophicans vasculare* the relatively frequent onset in the *menopause* seems worthy of mention [1911] The same is true of *acrodermatitis atrophicans* In this dermatosis which is not very rare in some parts of Europe, the females outnumber the males 2 1 [1913] There are some observations of acrodermatitis atrophicans in Graves disease [1914]

Acrocyanosis —*Erythema venosum* [1918] *Erythrocyanosis symmetrica* [1919] *Erythrocyanose symmétrique malléolaire des jeune filles*

Symmetrical sometimes circular palm sized cyanotic plaques almost exclusively occurring in young girls[1920] have been described under several names [1921] The plaques are mostly seen anteriorly or laterally on the lower legs less often on the inner aspects of the thighs right above the knees The lesions are bluish red sometimes with bright red (cinnabar) spots[1922] and some thin telangiectases The erythema vanishes on pressure The skin is taut and cannot be folded The lanugo has usually disappeared There is an ill defined deep firmness which gives a doughy impression though there is no pitting The lesions are cooler to the touch than the normal skin Superficial ulceration has been seen but this is rare [1920,1923] Local fat increase has been described [1924] There is only minimal nonspecific inflammation around the vessels Capillaroscopy reveals varicosities of the capillary veins and frequent spasms [1920] The course is an extremely chronic one The lesions appear in the winter time improve in summer to some extent and reappear with the first frost Like many lower leg conditions they are better after a night s rest and worse again in the evening The dermatosis is clinically closely related to chilblains from which it differs in the site and the accompanying circumstances which make an ovarian relation probable [1925] The patients are overwhelmingly *young girls* and women up to about thirty years of age

Children do not seem to become affected though they are very susceptible to chilblains Irregularities of menstruation [1926] obesity[1920] and other endocrine

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[1913] Bezecny R and Berlin F Ätiologie de Acrodermatitis atrophican Herxheimer Klin Wchnschr 12 276 277 1933

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[1919] Bolt F Erythrocyanosis cutis symmetrica Klin. Wchnschr 1 578 590 1922

[1920] Ulimo A Érythro-cyanose symétrique sus malléolaire des jeunes filles Thè de Strasbourg 1929

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[1923] Baer T Stauungsdermatose Zbl 43 603

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[1925] Klining Akrocyanosis cruris Zbl 32 416 1930

[1926] Sellei and Liebner Erythrocyanosis extremitatis chronica Arch. f Dermat u Syph 156 2 7 1928

stigmata like hyperidrosis of palms and soles. Marañon's[?] main hypogenital, dry skin, goiter[?] and adrenal hypotension[?] have often been observed.[?] The condition has also been seen after castration.[?] Estrogen therapy and thyroid have been helpful in many cases. Yet no entirely convincing endocrine relationship has so far been established. Tuberculosis[?] has been considered since some cases developed into tuberculosis indurativa.[?] The condition seems to be rarer in the United States than in the corresponding climates in Europe.

[?] Marañon, G.: The Hypogenital Hand (Akrocyanosis) ... [illegible] 1931, [illegible]

[?] Thomas, J.: L'acrocyanose ... à la période ... Arch. f. Med. [illegible] 1931, [illegible]

[?] ... J.: L'acrocyanose permanente des jeunes ... Arch. ... méd. d. enf. [illegible] 1934, [illegible]

[?] Galant, J. S.: ... Arch. f. path. Anat. 287: [illegible] 19[illegible]

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Chapter XXVII

AGEING*

Senile *atrophy* of the skin starts shortly after the age of forty[1935] The epidermis becomes thinner at the expense of the lower strata The horny layer appears looser The mitoses in the basal layer become scarcer or disappear completely and the cells of the basal and prickle cell layers show perinuclear vacuolization The stratum granulosum is hardly discernible[1 87] The papillae flatten and lose their elastic fibers The collagenous fibers grow thinner and stain poorly The elastic fibers show clumping shortening thickening and irregular positions together with marked hyperplasia especially in the face and neck This hyperplasia of the elastic tissue may account for the yellowish tinge of the face and hands in some old people[1936]

Elacin collastin and collatin are often present[1937] The peculiar accumulations of elastic fibers in the facial skin known as elastica mimica[1490] which develop at puberty and reach their highest development at thirty are definitely regressive at forty At sixty the alterations of the elastica are marked[1938] The elastic fibers of the blood vessels especially of the elastica interna participate in the changes The senile changes in the elastic fibers seem to depend on exposure to light and elements since they were not found in unexposed skin of old people[1939]

Extravasation on slight trauma (*purpura senilis*) is common

Severe arteriosclerotic changes may be observed along with corresponding senile changes in other organs

The *sebaceous glands* are reduced in number and they show certain qualitative changes In the face especially on the nose and forehead hyperplasia of the sebaceous glands is common after the age of forty The hair follicles are often found without hair and the musculi arrectores pilorum are usually atrophic The subcutaneous fat shows degeneration[1 67] The water content of the senile skin is reduced[1935 1940] and the rate of insensible perspiration is lower than in young subjects[1941] The capillary reactivity to mechanical and other stimuli

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* See tal l at th nd of the book

[1935] Evans R Cowd y E V and Wi lson P E Ag i g of Human Skin Influence of Dermal Shrinkage on Appearance f Epid rmis in Young and Old Fixed Tissu s Anat Rec 86 545-565 1943

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[1940] Bürger M and Schlomka G Ch mische Gewebsu tersuchung f0 die Alte nsforschung Klin Wchnschr 7 1944 19.. 19 8

[1941] Burch C E Cohn A E and Neumann C Rat of Wate Loss From Fing Tips and Toe Tips in Normals Senlles etc Am Heart J 22 185-196 1942

is slow in response and slow in return to the normal status.[1932,1933] Cavallucci, who systematically studied the *physiological reactions* of the senile skin in comparison with that of the middle aged, found red dermographism delayed and urticaria factitia less frequent and less pronounced. Marinon's sign (see thyroid), the pilomotor reaction and the urticarial intracutaneous morphine reaction are also less marked. Senile atrophy causes decrease of the sensitivity to touch, pain and temperature. The fact that old people suffer from cold more than young persons is not due to increased sensitivity but to other, probably vascular, factors.



Fig. 233. Purpura senilis

The cutaneous manifestations of ageing are of practical importance for the *objective determination* of the age.[1934,1935] At the age of 20 the facial skin is still free of wrinkles. The cheeks are rounded so that the mouth and nose appear small. At 25 the forehead and the lower lids show the first wrinkles and the nasolabial folds become apparent. The veins of the back of the hand begin to show.[1935] At 30 "crow's feet" appear at the lateral angles of the eyes. The beard growth is most vigorous between 30 and 40. At this age men often become more hairy on the chest, arms and the dorsa of the hands. The occipital hairline loses its sharpness.

The thirty fifth year usually marks the first folds in front of the ears (Nudeshdin after Sebastiany[1934]). These preauricular wrinkles increase in length more than in depth so that some criminologists have attributed much importance just to the length of these folds.[1935] Graying of the hair at the temples and a less

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[1932] Bettmann, S.: Altersveränderungen am Gefässendabschnitt der Lippenschleimhaut. Ztschr. f. Anat. u. Entwcklungsgesch. 93: 600-677, 1930. Zbl. 37: 600.

[1933] Cavallucci, U.: Anatomia e fisiopatologia della cute. Reattività della cute senile. Gior. ital. di dermat. e sif. 75: 876-879, 1934.

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rosy and more ruddy hue of the cheeks may become noticeable in the fourth decade The age of graying varies widely A familial factor can often be recognized

A person of 40 already has most of the typical wrinkles The preauricular wrinkles are now multiple and extend upward to the upper level of the tragus The cervical folds which run from the chin down to the jugulum may be seen in lateral light

At 45 the suborbital wrinkles become more marked In light coming from the side the cervical folds can now be clearly seen The lips start to become thinner In a fat person the double chin is marked and in a lean person the cervical skin becomes too wide[1945] The eyebrows may become bushy or at least a few long hairs may grow



Fig 234



Fig 235

Fig 234 —Female aged 65 years Long ear preauricular wrinkles
Fig 235 —Cervical and other folds and wrinkles

In the early fifties all the wrinkles grow deeper The hands become wrinkled Small wrinkles of the bridge of the nose, of the ear lobe and of the chin are present The entire skin is now relatively dry The graying of the hair can no longer be concealed by pulling out of the white hairs

Senile hyperpigmentation starts around 55 Wrinkles on the bridge of the nose the ear lobes and the chin become marked The longitudinal cervical folds are accented The rhomboidal crossing folds in the nape of the neck (Cutis rhomboidalis) are seen in some men especially those who live an outdoor life

In the sixth decade the teeth appear to be longer because of atrophy of the alveolar ridge

At 60 the first radial wrinkles around the mouth appear on the upper lip. The cheeks become loose and droopy. The glans penis becomes smaller and the penile skin wrinkled and darker. The pubic hair in the male appears thin and less curly, though possibly spread over a wider area than in younger years. The scrotum is longer and more flaccid, and fails to contract on exposure to cold, probably because of atrophy of the tunica dartos.





Fig. 36. Fig. 37.

Fig. 36. Male aged 87 years. [illegible] pre-auricular fold. Pigmented spot.
Fig. 37. Vermilion of lips has [illegible] appeared. Wrinkles across lips.

In the female analogous regression of the labia majora takes place. The subcutaneous fat is often accumulated around the hip, leaving the extremities and the chest relatively lean. The formation of the arcus senilis corneae begins.

Around 65 the hair growth in the ear ducts, the nostril and on the nape of the neck becomes more conspicuous in men as well as in women. The bristly hypertrichosis on the chin is often marked in the female sex.

At the age of 70 the facial wrinkles are often found crossing each other. Sometimes they form a netlike pattern or a papyraceous wrinkling like that seen in castrates. Senile pigmentations have increased. The skin is thin and a fold lifted from the back of the hand returns but slowly to the normal position. The head hair is usually thin or has disappeared. Complete senile baldness is occasionally seen in women also.

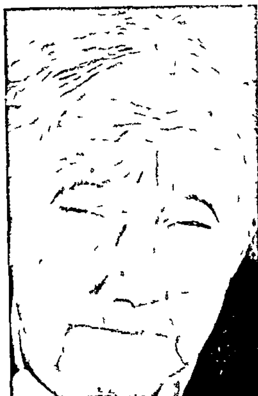


Fig 238 —Female ag d 80 years All wrinkles are develop l Drooping upp lid Ve mili n of th lips ha disapp ared



Fig 239 — Male aged 76 y rs Senile atrophy of th ski



Fig 240 — Female aged 83 years Senile keratoma basal cell epithelioma of naso-labial fold Crossing wrinkles around the mouth Vermilion border has disappeared



Fig 241 — Male aged 86 years The long ear of old age

The thinning of the lips is completed at 75 so that hardly any vermilion can be seen The thin mouth appears longer and sunken because of the atrophy of the alveolar ridges and the loss of the teeth The backs of the hands are wrinkled like thin paper



Fig 24 — Mal ag d 7 years I ong t th of old age



Fig 243 —Senil pigm ted spot

The eighties are characterized by the tired expression of the eyes caused by *the drooping upper lid (senile ptosis)* *The radial wrinkles around the mouth* are conspicuous The cervical folds which appeared long before are very marked The ears not only appear longer but are actually larger and flabby The nose



Fig. [illegible] [illegible]enile keratom[illegible]



Fig. 45 — [illegible]e[illegible]ll hemangioma of the v[illegible]rmilion border

seems to be larger The skin of the back of the hands is now very yellowish thin and pigmented and the underlying fat has practically disappeared The muscles have atrophied The knuckles and small joints are very marked There are not only transverse wrinkles but also longitudinal folds The hand gives a bony impression

It should be kept in mind that all signs of ageing are subject to relatively wide variations However the evaluation of the appearance of wrinkles is a fairly reliable guide to objective age estimation

Old age predisposes to a great number of *dermatoses* Epitheliomas keratoses pigmented spots small hemangiomas especially the hemangioma of the vermilion border of the lips xanthelasmas of the eyelids sebaceous adenomas pendulous fibromas (acrochordon) and other neoplasms are common The dryness of the skin caused by the reduction of the sebaceous glands is often troublesome Pruritus senilis is another common and stubborn skin trouble of old age probably caused by the vascular changes Purpura senilis (Bateman after Pasini[1946]) is found on the acral and extensor surfaces On slight trauma or even without it telangiectatic and purpuric spots appear and undergo the usual color changes leaving long lasting pigmentations Such spots are often found on the back of the hands where the senile atrophy is pronounced and the exposure to slight trauma is greater than of other parts Purpura senilis does not disturb the well being of the patient

Thickening and opacity or dark discoloration of the toe nails is a common sight in old people The rate of growth of the hair and of the nails is substantially reduced [1936]

[1946] Pasini A Purpura Senilis Monatsh f prakt Derm 43 401 1906

CHAPTER XXXIII

METABOLIC DISORDERS

Diabetes

The Blood Sugar Test.—With the increasing knowledge of diabetes, particularly with the development of the methods of blood sugar determination, a large number of investigators have studied dermatoses in hyperglycemia as well as the presence of hyperglycemia in dermatoses. Today it is generally held that the absence of sugar in the urine does not rule out diabetes. The determination of the blood sugar level after fasting and after a measured intake of sugar has become an important diagnostic procedure, and many investigators have tried to correlate dermatoses and the blood sugar.

The normal fasting values given by different authors vary considerably, but 80 to 120 mg. in 100 c.c. of blood may be considered normal. The gravimetric methods (Bang, Hagedorn and Jensen) give lower values than the colorimetric methods (Folin and Wu). Populations with a diet rich in carbohydrates have a higher average blood sugar level than groups whose carbohydrate is lower.[1047] For the determination of sugar tolerance some authors prefer the intravenous injection of glucose to the oral administration, but today the drinking of 100 grams of dextrose in water after twelve hours of fasting and the determination of the blood sugar after one-half, one, two, and three hours is a standard method.[1047] It not only avoids the intravenous injection but duplicates the normal manner of sugar intake. It must be emphasized that disorders of the endocrine-sympathetic system, menstruation, exertion during the test, and under- or overfeeding with carbohydrate during the days before the test may influence the blood sugar curve. Urbach considers a blood sugar tolerance curve characteristic for diabetes only if:

(1) The highest point of the curve is reached later than one-half hour after the ingestion of the sugar.
(2) If the course of the curve is protracted enough to form a flat curve instead of the normal steep type.
(3) If the fasting value has not been reached again within three hours.

Blotner[1048] considers potential diabetes if the peak of the curve reaches 165 mg. per cent in one-half or one hour, and he diagnoses diabetes when the blood sugar exceeds 170 mg. and some or all of the urine specimens contain sugar.

Carbohydrate Metabolism in the Skin.—Urbach and his collaborators designed a method of examining the skin sugar content which requires only a

[1047] Urbach, E.: Beiträge zu einer physiologischen und pathologischen Chemie der Haut. Isolierte kutane Glykohistächie als Ursache chronischer Dermatosen. Med. Klin. 29: 359-360, 1933.

[1048] Blotner, H.: Glycosuria and Diabetes Mellitus in Selectees. J.A.M.A. 131: 1109-1114, 1946.

very small quantity (30 to 40 mg) of skin taken with an electric biopsy punch of 3 5 mm [1949, 1950]

The skin sugar content in laboratory animals varies considerably In the rabbit it reaches 143 per cent of the blood sugar, the highest of the known values The normal human fasting skin sugar amounts to only 58 per cent of the blood sugar [1950] These findings are remarkable because the blood sugar levels in man and in laboratory animals do not differ greatly both being between 83 to 111 mg per cent The e figures refer to the so called free sugar The bound sugar which can be obtained only by acid hydrolysis is fifteen times higher The skin makes up 16 per cent of the body weight Only the muscles weigh more of all the organs Considering the high sugar content together with the fact that the skin weighs one sixth of the body and three times more than the liver it is apparent that the skin is likely to be important in the sugar metabolism Urbach[1947] considers a fasting skin sugar level of more than 68 mg per cent as pathologic He showed that the curve obtained by skin sugar determinations after oral administration of 100 grams of dextrose imitates the blood sugar curve but it requires about one half hour more to reach the maximum and about one hour more to reach the fasting value again Diet low in carbohydrate preceding the test causes a lower fasting level of the skin and blood sugar and a much higher maximum level of the skin and blood sugar curves than a high carbohydrate diet A diet high in fat lowers the sugar content of the skin while the blood sugar level remains the same [1950] In the depancreatized dog the skin sugar increases much more than the blood sugar

In diabetics the $\frac{\text{skin sugar}}{\text{blood sugar}}$ ratio is high Following the tolerance test the skin sugar is almost doubled and the time required for return to normal may be longer than five hours [1950] This demonstrates that the diabetic skin stores sugar for a long time and would explain its often observed susceptibility to infections Storage decomposition and excretion of sugar seems to be a normal function of the skin [1951]

Urbach found in diabetics with dermatoses such as furunculosis hydradenitis eczema urticaria and pruritus the skin sugar higher (85 mg per cent) than in diabetics without dermadromes (66 mg per cent) in spite of about equal blood sugar levels Thus in the diabetics with dermadromes the ratio $\frac{\text{skin sugar}}{\text{blood sugar}}$ seems to be higher than in those without dermadromes In animals poisoned with extremely high doses of insulin the skin sugar never fell below a certain level In diabetic patients diet and insulin could not lower the skin sugar below 39 mg per cent Pillsbury[195] made the existence of an autonomous carbohydrate metabolism in the skin still more evident by studying lactic acid

[1949] Urbach & Fantl De Zu kerg halt der normalen Haut Biochem Ztschr 196 474 1928
[1950] Urbach E and Lentz J W Carbohydrate Metabolism and the Skin Arch Dermat & Syph 52 301-316 1945
[1951] Folin O Trimble H C and Newman L H The Distribution and Recovery of Glucose Injected Into Animals J Biol Chem 75 63 281 1927
[1952] Pillsbury D M The Intrinsic Carbohydrate Metabolism of the Skin J A M A 96 426-432 1931

formation in the skin. He found this characteristic product of carbohydrate metabolism to be normally present. The skin contains several enzymes concerned with the splitting of carbohydrates. The stages of this process are the same as in the muscle and in the liver.[1953]

Urbach and his associates[illegible] discovered what they called *isolated skin diabetes* or cutaneous glycohistechia. They found that there exists in some cases a high fasting skin sugar and a flattened skin sugar tolerance curve in the presence of normal fasting blood sugar and a normal blood sugar tolerance curve. The patients suffered mostly from chronic eczemas, furunculosis and vaginal or anal pruritus. A certain number of them responded well to insulin and a diet low in carbohydrates, clinically as well as in the fasting skin sugar and in the skin sugar tolerance curve. No transition of skin diabetes into frank diabetes has been observed.[illegible] This "skin diabetes" has not become widely known, mainly because of the necessary punch biopsies and the new analytic methods.



Fig. [illegible]. Skin diabetes with ulcerations. (Urbach.) (From Urbach, F.: Skin Diseases, Nutrition and Metabolism. Grune & Stratton, Inc.)

Besides the excised skin, sweat and serum from artificial blebs have been studied with regard to their sugar content. Urbach emphasizes that the analysis of bleb serum is no substitute for that of skin tissue. The blister serum sugar is higher than the skin sugar. Its changes after sugar ingestion are similar but

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[1953] Wohlgemuth, J.: Über den Kohlehydratstoffwechsel der Haut. Deutsch. med. Wchnschr. 57: 1814-1815, 1931.

[1954] Moncorps, C.: Kohlehydratstoffwechsel und Haut. Jahreskurse f. ärztl. Fortbild. 22: 7-36, 1931.

[1955] Urbach, E.: Isolierte Glykohistechie als Ursache chronischer Furunkulose. Zbl. 44: 50?, 1933.

[1956] Urbach, F., Deplsch, F. and Sicher, G.: Isolierter hoher Hautzucker bzw. Hautdiabetes. Klin. Wchnschr. 16: 45, 1937.

[1957] Urbach, F.: Skin Diabetes. J.A.M.A. 129: 438-440, 1945.

slower than those of the blood sugar [1958, 1959] In persons who are intolerant to sugar the sweat contains an abnormal amount of sugar After ingestion of much dextrose the sweat sugar may increase 100 to 150 per cent or more even 300 to 400 per cent [1960] The sugar from evaporated sweat may accumulate on the skin and cause irritation pruritus and folliculitis just as the sugar does in persons who are occupationally in contact with sugar Carrié and Koenig[1961] measured the sugar accumulated on the skin It reaches its maximum four days after a bath the armpits collecting more sugar than open areas The sugar on the skin is much higher in diabetics than in normal persons The sweat sugar values determined by reduction only have been considered more recently as being much too high [1962]

Another approach for testing the skin in diabetes has been advanced by Seelig [1963] Using the method of McClure and Aldrich he compared the time which a wheal produced with 5 c c of 1 per cent aqueous glucose solution needed to disappear compared with one produced with 9 per cent saline solution In diabetics and glucose wheals disappeared more quickly yet never before the controls with saline wheals This seems to indicate an increased avidity of the diabetic skin for glucose

The majority of the investigators tried to find out how the blood sugar influences the skin The possibility that the *skin* or at least pathological changes of the skin might *influence the blood sugar* has been given much less attention

Skin irritations of many kinds e g from croton oil[1964] injections of saline foreign proteins and olive oil increase the blood sugar within certain limits according to the intensity of the inflammation [1954, 1965, 1968] The extract of artificially inflamed skin injected into normal rabbits raises the blood sugar level to a larger extent than extracts of normal skin The increase is higher in rabbits with already inflamed skin than in rabbits with normal skin It is interesting that high blood sugar curves in psoriasis may become normal after the skin symptoms have been cleared by local treatment [1969] Marchionini and

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[1958] Ferrari A V Raffronto fra il contenuto in glucosio del sangue e d l liquido di bolla dopo la somministrazione di zucchero p r via orale ad individui non malati Dermosifilografo 6 293 314 1931 Zbl 38 765

[1959] Bronzini M La funzione r ale in al uni dermopa i oti Arch Ital di de mat if 7 65-81 1931 Zbl 38 764

[1960] Usher B and Rabinowitz I M Excretion of Sugar in Sweat Arch. D rmat & Syph 16 706 713 19 7

[1961] Carrié C and Koenig R Ueber den Zuckergehalt auf der Haut bei Normalen und Diabetikern Arch f D rmat u Syph 173 611 614 1936

[1962] Schulze W Sugar Content of Skin and Sweat Comparative Study of Diabetic and Non diabetic Subject Arch f Dermat u Syph 181 471-485 1940

[1963] Seelig S F Diabetes Diagnosis Intradermal Skin Tests Guy s Hosp Rep 88 210-217 1938

[1964] Pi cussen L Effect of Irradiation With Monochromatic Light on Blood Sugar and Lactic Acid in Rabbits Bioch m Ztschr 272 354-358 1934

[1965] Ayres S Jr Glucose Tolerance Reactions in Eczema Arch D rmat & Syph 11 623 636 19 5

[1966] Narahara K Experimental Studies on Skin Sugar Jap J Dermat & Urol 30 1113 1128 1930 32 87 101 1932 639-653 193 340-366 1932 Zbl 38 765 42 181 43 511

[1967] Miyak I Einfluss von Dermatitis—Hautextrakt auf Blutzucker Jap J Dermat & Urol 31 1309-13?? 1931 Zbl 40 303

[1968] Marchionini A and Hov lbor K Ultraviolettbestrahlung und Kohlehydratstoffwechsel Klin. Wchnschr 14 135? 139? 1935

[1969] Moncorps C Bohnstedt R M and Schmid R Sugar and Glutathion Content of Skin Arch f Dermat u Syph 169 67 76 1933

Hövelborn[1967] studied the influence of ultraviolet light on the carbohydrate metabolism. At the height of the erythema the fasting value of the blood sugar drops and the blood pressure decreases. This, together with the increase of blood diastase, points to one or several insulin-resembling[1968] substances in the skin, produced either in the skin or in the pancreas on stimulation from the skin. Moncorps[1969] also found a substance in the skin which raises the blood sugar.

Incidence of Dermatoses in Large Groups of Diabetics.—Greenwood[1970] compared the skin of 500 diabetic and 500 nondiabetic general hospital patients. About 25 per cent of the diabetics either had or had had skin diseases, mainly pruritus (7 per cent), eczema, epidermophytosis, furunculosis and carbuncle (2 per cent) and xanthoma palpebrarum (18 per cent). The patients with a dry skin (20 per cent) seemed to be more apt to develop dermatoses than those with a moist skin. The figures were generally higher than in the nondiabetic group. The total percentages in the control group are meaningless because of the difficulty to obtain reliable figures for epidermophytosis. Tauber[1971] found among 514 diabetics, most of whom were hospital patients, gangrene in 18 per cent, ulcers in 4.3 per cent, furuncles and carbuncles in 3.8 per cent, infected hands and feet in 23 per cent and pruritus vulvae et ani in 0.8 per cent. This and other lists show that the recorded incidences vary widely even in large groups, probably due to the selection of the studied series. Statistics of hospitalized diabetics are apt to carry a high percentage of severe complications, especially gangrene, which are much rarer in ambulatory groups (Lane's series given in Greenwood[1970]).

How often is a dermatosis the presenting symptom of diabetes? Every experienced dermatologist will remember with satisfaction the cases of perioral eczema, balanitis or pruritus in which he first made the diagnosis of an underlying diabetes. In the large material of the Berlin University Skin Clinic 27 out of 1,000 patients were diabetics and only 13 per cent of them knew of their disease. In the others, their diabetes was diagnosed by the dermatologist. Among the diabetic skin patients of the Berlin Clinic 59 per cent had eczema (one fifth of these eczema of the genital region) and 22 per cent balanitis. These patients represent a group with uncontrolled diabetes.

The degree of control of the diabetes is probably the main factor which influences the incidence of dermadromes. The whole dermatological aspect of diabetes has changed since the introduction of insulin. In examining about 200 diabetic patients, most of whom were well controlled, the author was surprised to see how rare were even those skin diseases which are generally considered typical of diabetics. Epidermophytosis was seen to be neither more common nor more severe than in nondiabetics. Gangrene, furunculosis and carbuncle were rare, about 1 per cent. The most common skin change in the controlled diabetic is a slight yellow discoloration, probably due to minor degrees of carotenemia (Xanthosis diabeticorum).

[1970]Greenwood, A. M.: Skin in Diabetes, 500 Cases, J. A. M. A. 89: 774-776, 1927.

[1971]Tauber, E. B.: Hyperglycemia in Diseases of the Skin, Arch. Dermat. & Syph. 27: 198-205, 1933.

Mycoses —Greenwood[1970] found epidermophytosis in 40 per cent of his series of 500 diabetics Greenwood and Rockwood[1971] found clinical evidence of fungus infection in the interdigital spaces of the feet in 70 per cent of diabetic patients their diabetes being generally uncontrolled All thickened and opaque



Fig 47 —Epidermophytosis in a diabetic patient

nails were found to be infected No relationship to the blood sugar level could be established Percentages of other authors vary widely (see table in Gray and Close[1973]) Because of the great differences in the incidence in normal control groups it is difficult to state whether the incidence in diabetics is actually higher than in comparable normal groups Many authors[1974] emphasize the importance of the nails as a source of reinfection

The importance of *mycotic foot infections* in diabetics lies in the danger of more severe infections complications and gangrene The clinical aspect of epidermophytosis in diabetics does not seem to have special features

Every dermatologist has seen in obese women the characteristic though not very common picture of intertriginous genito inguinal and inframammary dermatitis often caused by *monilia* This bright red sharply bordered intertrigo surrounded by small pustular satellites is very suggestive of diabetes Oral moniliasis (thrush) is common in infants but is rare in adults If it occurs urine

[1971] Greenwood A M and Rockwood E M Skin in Diabetic Patients Arch Dermat & Syph 21 96-107 1930

[1973] Gray H and Close W E Chiropody and Diabetes M Rec. 154 445-449 1941

[1974] Kelly H J Significance of Dermatophytosis (Cause of Gangrene) Pennsylvania M J 41 581-586 1938



Fig. 214. Obese diabetic. Intertriginous moniliasis of the groin



Fig. [illegible] Obese diabetic. [illegible] framammary moniliasis



Fig 2 0 – Inframammary moniliasis in an ob e diab tic woman ag 1 0 yea



Fig 251 —Fro io int rdigitalis in a diabetic woma

and blood should be examined for sugar.[1975] Yeast infections of the hands, feet and particularly of the vulva occur mostly in uncontrolled diabetics.[1976] Proper management of the diabetes without local treatment can control the infection. This indicates the specific influence of the diabetes.



Fig. 23. Moniliasis in diabetes. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Diabetic vulvovaginitis is usually a mycotic infection.[1977, 1978] It is encountered in about 50 per cent of women with diabetes. The vulva appears slightly swollen and tender, with a reddish blue color and a thin grayish surface. Abrasions and excoriations together with a sensation of heat cause much discomfort. The inflammation is usually limited to the moist surfaces but may extend to the mons

[1975] Christoph: Soor und Diabetes, Zbl. 22: 606, 19 7.
[1976] Traut, H. F., White, L., and Hemphill, R. B.: Moniliasis of the Skin in Diabetes, J.A.M.A. 102: 1290-1292, 1934.
[1977] Hesseltine, H. C.: Diabetic or Mycotic Vulvovaginitis, J.A.M.A. 100: 177-178, 1933.
[1978] Hesseltine and Campbell: Diabetic or Mycotic Vulvovaginitis, Am. J. Obst. & Gynec. 35: 272-283, 1938.

veneris anus and crural folds Small white areas (thrush spots) on the labia minora contain yeasts Glucose applied in powder or solution is supposed to cause a flaring up of the vulvitis in mycotic infections as compared with vulvitis of other causes Hesseltine[1977] speaks of mycotic vulvitis rather than of diabetic vulvitis because it is not the irritation from the sugar containing urine but the infection that causes the vulvitis The sugar fermenting yeast of course finds a good medium in the glucose containing urine and tissues Optimal growth of yeasts and also of staphylococci is found on media with 150 to 200 mg per cent of sugar This figure corresponds well to the sugar contents of serum in many diabetics[1979]

Diabetes was the cause in 26 of 31 consecutive patients with pruritus vulvae[1793] Fifteen of these 26 diabetics failed to show sugar in the urine Only blood sugar tests and a detailed history established the diagnosis These women were between thirty and fifty years of age Such cases may often be treated as menopausal pruritus if no finer diagnostic test than the unreliable urine test is used



Fig ? 3 — Diabetic balanitis and ulcer of glans penis (From Urbach E Skin Diseases Nutrition and Metabolism Grune & Stratton Inc)

Diabetic *balanitis* is much rarer than vulvitis the ratio being 1 3[1980] It occurs less often in circumcised men whose glans penis is dry and does *not* give the yeasts such a favorable moist medium Among 147 cases of diabetic balanitis treated in the University Skin Clinic in Berlin there was not one in a circumcised man

Eczema surrounding any not only the urethral and anal orifices is always suggestive of diabetes Eczema around the eyes may be caused by *sugar containing* tears perioral eczema and perlèche by *sugar containing* saliva

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[1979] Engelhardt W Haben die beim Diabetiker gehäuft auftretenden Infectionen durch Staphylokken und *Hefen* ihre Ursache in dem erhöhten Haut und Schweisszucker? München med Wehnschr 80 2037 2038 1933

[1980] Dalhöfer A Hautkrankheiten und Diabetes mellitu Inaug Di Berlin 1935

Vascular Disease.—Vascular disease of slight degree is extremely frequent in elderly and middle aged diabetics. Abnormally low temperature, pallor or cyanosis of the feet have been observed in approximately one half of 124 patients.[1991] The capillary fragility of diabetics, as demonstrated by the tourniquet test, is greater at each decade than in nondiabetic groups.[1992] Gottron emphasizes the increased capillary reactivity in diabetes.

In many cases, gangrene of the toe or foot can be traced to minor skin ailments like epidermophytosis, interdigital fissure, ingrown toe nail, infected corns and calluses, and small injuries from self treatment.[1994] All these conditions should receive particular attention. Many of them are caused by improper and



Fig. 54. Diabetic gangrene.

tight shoes. Systematic foot hygiene in diabetics has been advocated by many physicians having wide experience in the management of diabetes. The institution of special foot clinics in large centers has undoubtedly helped to decrease the number of serious complications.[1993,1994]

[1991]Nall, M. Diabetes Mellitus as Observed in 100 Cases for 10 or More Years. Peripheral Vascular Findings in 60 of These Cases. Am. J. M. Sc. 209: 23, 1945.

[1992]Beaser, S. B., Rudy, A., and Seligman, A. M.: Capillary Fragility in Relation to Diabetes, Hypertension and Age. Arch. Int. Med. 73: 18, 1944.

[1993]Joslin, E. P.: Treatment of Diabetes. Philadelphia, 1937, Lea & Febiger.

[1994]Brandaleone, H., Standard, S., and Ralli, E. P.: Prophylactic Foot Treatment. Ann. Surg. 105: 120-124, 1937.

In these foot clinics the patients are educated to follow a daily morning routine of a warm foot bath without or with little soap followed by an alcohol rub and dusting with boric acid foot powder They are advised to massage their feet with lanolin at night Epsom salt should not be used for the foot baths because it makes the skin dry Commercial corn remedies should not be applied and blisters not opened The toenails should be clipped properly Foot exercises consisting of a series of movements of the toes feet and legs are considered important if any vascular disease is present All exercises are done six times and if there is a tendency to coldness the exercises should be done twice a day An important part of the exercise is the alternating raising and hanging down of both legs for three minutes Contrast baths of the feet are recommended The patient should begin with 105° F (40 5 C) and change five times to 50 (10°C) keeping the feet one minute in each bath and finishing with the warm bath He should keep his feet warm with stockings and not with hot water bottles Expert care should be taken of abnormal toenails calluses corns and mycotic infections Extremely well fitting shoes and comfortable stockings are important No walking barefoot no circular garters or bandages and no metal arch supporters are permitted

Impending gangrene will usually be diagnosed by observing the following signs [1985]

1 The pulsation of the peripheral arteries especially of the dorsalis pedis Both sides must be compared Good pulsation does not preclude gangrene of a toe because a more peripheral part of the artery may be occluded Absence of pulsation does not always mean impending gangrene because a collateral circulation may develop

2 If the color of the elevated and dependent extremity remains the same the prognosis is relatively good whether the pulse is palpable or not Pallor on elevation slow recoloring on return to horizontal position and purplish discoloration of the dependent extremities means extensive circulatory disturbance The level of the abnormal discoloration indicates the approximate level of occlusion

3 The skin temperature is taken with special thermometers or by running the hand (ulnar side) from the thigh to the toes One should always compare both sides A gradual fall of the temperature is normal but a sudden change is of the same significance as a level of discoloration

4 The histamine test consists in scratching through a drop of histamine solution on both sides and on various levels or in intradermal injections The wheal and flare formation is supposed to be in inverse proportion to the degree of circulatory impairment

Diabetic gangrene does not occur in the lower extremities only and it is not entirely a disease of old age Gangrene of many other parts of the body surface are on record On the face gangrene may at first resemble erysipelas and later turn into a deep slough frequently with a fatal outcome particularly

[1985] Grodinsky M Infection and Gangrene of Extremities Diagnosis and Treatment Am J Surg 42 339-349 1938

PLATE IX

1 Pellagroid pigmentation of the hands, atrophy and senile purpura. Ecchymoses appear on slight trauma, e.g. percussion with rubber-tipped hammer.

Necrobiosis lipoidica diabeticorum (Urbach-Oppenheim). (Courtesy Dr. L. Babalian.)

3 Diabetes. Infected toenail and early stage of gangrene.

4 Diabetes: three days later gangrene seems localized.

5 Female aged 21 years. Xanthoma diabeticorum, unusually large lesion. Blood cholesterol 810 mg. per cent.

6 Female aged 21 years. Xanthoma diabeticorum.








PLATE IV

if the cheek is involved[1986] Loss of lips, ears, and particularly of the nose as well as perforation of the septum and of the palate have often been reported Gangrene of the penis of the vulva and[1987] of small and large superficial or deep areas of the skin are known The superficial gangrene which occurs in small patches is called ecthyma Though rarely diabetic gangrene may occur very early in life Trauma plays a role in unusual sites of diabetic gangrene

The *treatment* of diabetic gangrene is mainly a surgical problem After drying of superficial necroses with subgallate of bismuth or other means the sores should be dressed with ointments containing as much cod liver oil as possible

In every case of beginning or impending gangrene pancreatic extract (Pancreatic hormone Grant or Sharp and Dohme s pancreatic tissue extract) should be given a trial One to 3 c c are given daily or on alternate days Padutin another pancreatic enzyme free preparation is given by injection and by mouth Wolffe[1988] recently reported 100 cases of gangrene that had received treatment with enzyme free pancreatic extract Eighty eight per cent of the beginning dry gangrene, and sixty three per cent of the more severe cases with not more than two toes involved were healed The majority of these cases were diabetics The pancreas contains a vasodilatory substance which is able to neutralize the rise in blood pressure produced by epinephrine It furthermore aids in fat metabolism by lowering the blood cholesterol and blood phosphatides This substance is not identical with choline nor histamine It may be identical or partly identical with the alcoholic fat and insulin free neutral pancreatic extract Lipocaic[1989] which lowers lipemia and allows depancreatized insulin treated dogs to survive for longer than two to three months without the feeding of fresh pancreas

Diabetic Ulcer —Trophic ulcer of the foot is not infrequently found associated with diabetes The diabetic ulcer is not different in its appearance from other trophic foot ulcerations It develops most often on the dorsum or the plantar surface of the big toe or at points of increased pressure The patients are often overweight rarely young Besides the care of the obesity exercises to improve the circulation and the topical application of cod liver oil are indicated Well fitting shoes and protection from cold are most important

Pruritus —Pruritus is especially in women[1970] such a common diabetic dermadrome that the urine should routinely be tested for sugar in all cases In all stubborn and unexplained cases blood sugar tests should be done More than fifty per cent of the ca es of pruritus sine materia show patho glycemic curves[1990] Besides the dietary and insulin treatment French authors have

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[1986] Millett J Diabetic Gangrene of Face 2 Fatal Cases J A M A 112 1143 1939

[1987] Fikin C W W Occurrence of Diab tic Gangre e in an Unusual Location J A M A 102 2187 1934

[1988] Wolffe J B Pancreatic Extract in Treatm nt of Gangrene Am J Surg 43 109-118 1939

[1989] Dragstedt L R Van Probaska J and Harms H P Sub tance in P ncreas (a Fat Metabolizing Ho mo) Which P mits Survi al and Prevents Liver Changes in Depancreatized Dogs Am J Physi l 117 175-181 1936

[1990] Campbell G Gordon R lation f Sugar Intolera e to Diseases of the Skin Brit J Dermat 43 297-304 1931

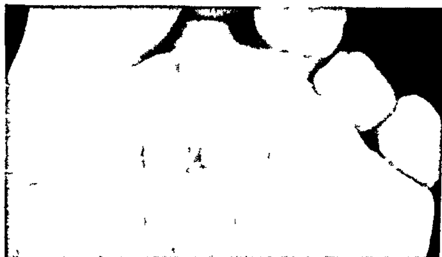


Fig L l u ilabetirum



Fig 256



Fig 57

Fig 6 L l us ilabetl un

Fig 7 Sa a aft r l w ks of diet an l In ull treatm t



Fig 8 — F lo t (uncontroll l diab te



Fig 239 I yod cms in u co trolled diab tes

reported successful x-ray therapy to the splanchnic areas.[1991] Spleen extract too has been advocated. Pruritus has been observed not only in hyperglycemia but also in hypoglycemia.[1992] Guldberg and Hannsdal treated such cases successfully with glucose injections and insulin.

Furuncles and Carbuncles have always been considered common in diabetes. This has been statistically confirmed by Greenwood[11 4] who found the incidence among 500 diabetics about twice as high as the general average of the hospital patients (2 per cent compared with 1.2 per cent) and 7 times higher when furuncles and carbuncles in the history were counted. Williams[1993] who tried to prove that pyogenic infections are no more common in diabetics than in normals, showed that boils and carbuncles occur in 2.3 per cent of hospitalized diabetics. This figure is about four times the percentage of the general hospital average.

Tauber[199] *who compared the incidence of furuncles and carbuncles in about* 500 hospitalized cases of diabetes with the incidence in 500 patients with normal or rather low blood sugar levels, found it to be twice as high among the latter. He also found a diet rich in carbohydrates (Wenckebach's diet), liver extract and daily intravenous injections of 500 c.c. of 5 per cent dextrose solution very helpful. Tauber's[199] figures have so far not been able to destroy the general and deeply rooted opinion that furunculosis is a frequent feature of uncontrolled diabetes.

Stomatitis.—Rudy and Cohen[1994] examined the mouths of 403 diabetics, 138 of whom were edentulous. In uncontrolled diabetes, particularly if oral hygiene is lacking, heavy supra- and sub-gingival tartar deposits are often formed. Gingivitis, swollen and bleeding gingival papillae and abscesses are common. The teeth, which are often decayed, become loose but should be saved. The dental condition improves if the diabetes is controlled. No surgical procedure should be done before control of the diabetes.

The tongue in uncontrolled diabetes is often dry and coated. The saliva has been found acid because of the high content of lactic acid. Thrush on the palate and pharyngitis sicca occur.

Pruritus of the Meatus Acusticus is sometimes very annoying and may *cause recurrent furunculosis of the external ear.*[1995, 1996]

[1991] Gouin, F., and Bienvenue, A.: Traitement des prurits diabétiques et des diabétides par la radiothérapie sympathique. Bull. Soc. franç. de dermat. et syph. 38: 376-379, 1931.

[1992] Harano, J.: Pruritus und Pruriginöse Affektionen in ihren Beziehungen zum Kohlehydratstoffwechsel. Acta dermat. 17: 24, 61-63, 1931; Zbl. 41: 78.

[1993] Williams, J. R.: Does Diabetes Mellitus Predispose the Patient to the Pyogenic Skin Infections? J.A.M.A. 118: 1357, 1942.

[1994] Rudy, A., and Cohen, M. M.: Diabetes Mellitus Oral Aspects. New England J. Med. 219: 503-508, 1938.

[1995] Mayr, E. H.: Diabetes und Hals-Nasen-Ohrenkrankheiten. Wien. klin. Wchnschr. 50: 1581-1582, 1937.

[1996] Hecht, B., and Dibold, H.: Relation of Diabetes to Suppurative Conditions in Ear and Nose. Wien. klin. Wchnschr. 49: 1341-1343, 1936.

Miscellaneous —*Dupuytren s Contracture* of the palmar aponeurosis and Peyronie s disease (induratio penis plastica) either alone or together are rare but have a definite relationship to diabetes Greenwood mentions the former having a percentage of 1 6 among his 500 diabetics About twenty per cent of the patients with Peyronie s disease (induratio penis plastica) which often accompanies Dupuytren s contracture are diabetics Nutritional deficiencies are reported to be more common in diabetes [1997]

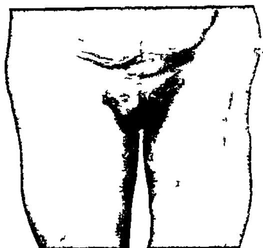


Fig 60 —At ophy of subcutaneous fat caused by i sulin injection (From Urbach E Skin Diseases Nutrition and Metabolism Grune & Stratton Inc)

Fat Atrophy —A peculiar sequel of diabetes is the fat atrophy at the sites of injections of insulin [1998, 1999] which occurs in about 7 per cent of the cases [2000] It is a harmless but sometimes disfiguring condition consisting of the localized loss of subcutaneous fat There is a decided feeling of looseness or emptiness in the subcutaneous tissues Several such pits the size of a silver dollar may coalesce Young diabetics with increased basal metabolism are especially inclined to develop this unusual response to insulin Shelly thinks that the insulin may cause a sudden release of glycogen from the muscle which helps to burn the fat [2001-003] Much rarer than fat atrophy is its opposite lipoma formation following insulin injections [2004-005]

[1997] Rudy A Unusual Case of D ficiency Disease in a Patient With Diabetes Mellitus Endocrinology 27 706 1940

[1998] Boborka C J Fat Atrophy From Injection of Insulin J A M A 87 1646 1926

[1999] D piech F Lokal Lipody trophi bei lange Zeit mit Insulin behandelten Fällen von Diabetes Klin W hnsch 5 1965 19 6

[2000] Alpert and Ferguson Local Fat Atrophy After Insulin Endocri ology 24 741 1939

[2001] Sh lly J A Insulin Atrophy (of Fat Tissue) Pennsylvania M J 40 347-348 1937

[2002] Winn tt E B Diabetes 360 Cases J Iowa M Soc 29 98-103 1939

[2003] Frei W Insulin Atrophy of Subcutaneous Fat Arch D rmat & Syph 37 534 535 1938

[2004] Row A H a d Garrison O H Lipodystrophy Atrophy and Tumefaction of Subcutaneous Tissu Due to Insulin Injections J A M A 99 16-18 193

[2005] Gellerstedt N Zirkumskripte Hyperplasie des subcutanen F ttgewebes als lokale Folge von Insulin Injection n Endokrinologie 10 417 1932

The patient in hypoglycemic shock perspires freely or even excessively while the skin remains dry in diabetic coma.[11, 1006]

Xanthoma Diabeticorum is a rare condition. Joslin[114] observed only six cases among 1,000 cases of severe diabetes. The patients are mostly younger males. The xanthomas appear quite suddenly, usually in large numbers on the extensor surface, the palms and the soles. The individual lesion is a small papule the size of a pinhead to that of a grain of wheat, rarely larger, red in color with a yellow center which looks pustular but is xanthomatous. They *often have an*



Fig. [illegible]. Female, aged [illegible] years. Xanthoma diabeticorum in a wa...

flammatory base and itch moderately. The histology shows intra and extracellular deposit of fat with more inflammation and fibrosis than in primary xanthoma. Thannhauser and Magendantz[1007] classify the diabetic xanthoma with the secondary lipidoses, which means they are a complication of a lipemia which can be caused by diabetes as well as by pregnancy, icterus, nephritis or other conditions. The diabetic xanthoma responds to diet and insulin (see also chapter on lipidoses).

Necrobiosis Lipoidica Diabeticorum (Oppenheim-Urbach).—It is remarkable that a conspicuous, characteristic and not extremely rare dermatosis *remained undescribed until 1929 when Oppenheim[1008, 1009] presented a case of a*

[1006] Wortl[illegible] J [illegible] Comm[illegible] Acu[illegible] Insulin Hypoglycemia J A M A 108 [illegible] 193[illegible]

[1007] Thannhauser S J and Magendantz H Different Clinical Groups of Xanthomatous Diseases [illegible] Cases Ann Int Med 11 160[illegible] 1746 1938

[1008] Oppenheim M [illegible] nicht beschriebene Hauterkrankung bei Diabetes mellitus (Dermatitis atrophicans lipoides diabetica) Wien klin Wchnschr 45 314-315 193[illegible]

[1009] Oppenheim M [illegible] nicht beschriebene mit eigentümlicher lipoider Degeneration der Elastica und des [illegible] Dermatose bei Diabetes mellitus (Dermatitis atrophicans lipoides diabetica) Arch f Dermat u Syph 166 576-583 1932

degenerative skin disease in a diabetic Urbach [2010] [012] in presenting another case three years later emphasized the presence of lipoid substances in necrobiotic foci He related these findings with the disturbance of the fat metabolism in diabetes

The lesions start as small red papules which grow slowly into irregular plaques from one to several inches in diameter In their mature stage they are waxy or mottled with a red yellow center The border is violaceous with a red or brown areola Subcutaneous nodules may be covered with normal skin The surface

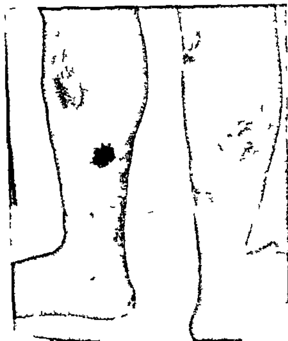


Fig 6 —Necrobiosis lipoidica diabeticorum (Urbach Oppenheim) (From Urbach E Skin Diseases Nutrition and Metabolism Grune & Stratton Inc)

of the older plaques is usually traversed by fine telangiectatic vessels The plaques are quite hard especially along the edges They are not elevated but the center of the lesions is flat or depressed The surface of the older lesions is shiny as if covered with collodion There is hardly any scaling Ulceration of the center may occur There is a tendency to heal slowly with an atrophic scar but this may take many years

The average number of lesions runs from a few to a dozen They are most often located on the lower legs Lesions on the hands and in other regions have been described but none on the face Itching or pain is never mentioned tenderness usually being the only complaint

[2010] Urbach E Lipoidstoffwechselerkrankungen der Haut Handb d H u Ch 12 2 3?-3 4 193
[2011] Urbach E Necrobiosis diabetica Ein neu diabetisch Stoffwechseldermatose Zbl 41 64 193?
[2012] Urbach E Eine neue diabetische Stoffwechseldermatose Necrobiosis lipoidica diabeticorum Arch f Dermat u Syph 166 273 293 193?

The histology of necrobiosis lipoidica diabeticorum is of great interest. The primary phenomenon seems to be an intense localized angiitis. There is an inflammatory thickening of the vascular walls which leads to gradual occlusion of the blood vessels, particularly of the small arteries, with slow necrosis of the areas involved. The collagenous fibers become waxy and swollen, and the nuclei disappear or stain but poorly with eosin. The elastic fibers deteriorate. Hemosiderin is present, explaining the brownish hue of the older lesions. The necrobiotic areas become impregnated with fat droplets which lie mostly, but not

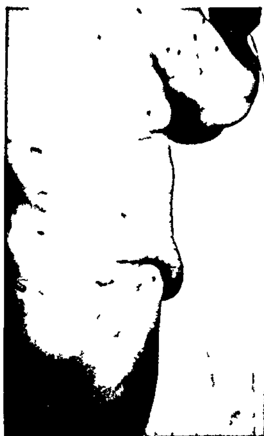


Fig. 63. Uncontrolled diabet..., obesity, hypert...sion, lichen urti...atus-like rash.

always, extracellularly, sometimes surrounding the vessels in a certain distance.[2013] Lymph capillaries stuffed with fat have been demonstrated. The droplets stain bright orange red with Sudan III, while the necrotic collagen is dull brown. Foam cells as in xanthomas, calcium deposits and giant cells have been observed,[2014] mainly in the periphery of older lesions.

[2013] Gottron, H.: Dermatitis Atrophicans Lipoides Diabetica, Med. Klin. 34: 145 190, 1938.

[2014] Nicholas, L.: Necrobiosis Lipoidica Diabeticorum With Xanthoma Cells (Case With Pulmonary Tuberculosis), Arch. Dermat. & Syph. 48: 606-611, 1943.

Both neutral fats [015] and doubly refractory cholesterol have been demonstrated High blood lipids, especially cholesterol have frequently been found The fat in the necrobiotic tissues is probably deposited from the blood

Ninety of the approximately one hundred cases so far presented were diabetics There is a preponderance of the female sex

The usual antidiabetic treatment does not seem to influence the condition but a diet low in fat as advocated in certain xanthomas has been recommended [2016 2017]

Diabetic carotenemia or *xanthosis* diabetica (see carotenemia) is probably the most common diabetic dermadrome It has long been considered harmless and explained by the fat and vegetable diet of the patients Recently Rabinowitch [018] found among 1 014 diabetics fifty nine cases of xanthosis thirteen of whom had never been on special diets prior to the detection of this skin condition The percentage of carotenemia in diabetics is probably much higher when the diagnosis is based on increased serum carotin and not only on clinical discoloration Being a frequent accompaniment of severe diabetes cardiovascular disease insulin edema resistance to insulin and hypercholesterolemia it suggests an unfavorable prognosis for the diabetes The disturbance of the lipid metabolism in diabetics the failure to synthesize vitamin A from its precursor carotin and possibly disturbed excretion of the carotin seem responsible for the accumulation of the lipochrome in the body

The Blood Sugar in Various Dermatoses

The blood sugar has been investigated in all common and many rare dermatoses Except for the established diabetic dermadromes the results have been meager In finding a high blood sugar level one should recall that inflammatory processes in the skin are able to raise the blood sugar [2019] The blood from capillaries of inflamed skin contains more sugar than from normal skin [0 0]

In groups of eczema patients [1965 1990 2021 20] a higher percentage of sugar intolerance has often been claimed but also denied [1971 023] Dermatitis intertriginosa seems more than other types of eczema correlated to sugar intolerance [024]

[0 5] Zeisl E P and Caro M R Necrobiosis Lipoidica Diabeticorum Arch Dermat **30** 796-812 1934

[1] Gross P and Machacek G F Necrobiosis Lipoidica Diabetica Arch Dermat & Syph **32** 491 1935

[17] Urbach E Cutane Lipoidosen Dermat Ztschr **66** 371-386 1933

[0] Rabinowitch I M Carotinemia and Diabetes Canad M A J **18** 527 530 1928

[20] Milbradt W Zu Blutzuckererhöhung der Dermatosen Dermat Wchnschr **94** 465-470 193

[1 20] Vitldana A and Gallia A Vergleichende Untersuchungen über den Zuckerspiegel in den Kapillaren pathologisch veränderter sowie normaler benachbarter Hautbezirke Dermat Wchnsch **94** 1255 1 61 1933

[21] Allison J R Hyperglycemia in Skin Diseases South M J **30** 738 742 1937

[1 22] Hermans E H and Hogerzeil H S Blutzucker und Hautkrankheiten Nederl tijdschr v Geneesk **75** 3908-396 1931 Zbl **39** 376

[23] Haldin Davis H and Wills L Abnormalities of Blood Sugar Content in Eczema Brit J Dermat **37** 364-370 19 5

Dry skin and *chapping* of the hands in cold weather should call attention to the possibility of a latent diabetes.[illegible] Chronic and unexplained eczema of the hands should be reason to search for diabetes.

It is an old experience that sugar and chocolate tend to make *acne* worse and that a diet low in sugar and starches is favorable for this condition. This is in accordance with Rosenfeld's[illegible] findings that sugar in the diet stimulates the secretion of the sebaceous glands more than fat. Schwartz,[illegible] Highman and Mahnkin found high blood sugar levels in fifteen out of about thirty acne cases and also a similar percentage in *seborrhea*. Recently Semon and Herrmann[illegible] reported good results in treating acne with small doses of insulin.[illegible] They refer mainly to cases with menstrual exacerbations, emphasizing that the blood sugar tolerance curve during menstruation is flattened, reaching the fasting value more than three hours after the sugar intake. Many authors[illegible] more or less deny the relationship of acne and hyperglycemia. Lately healing of acne during hypoglycemic shock therapy of psychoses has been reported.[illegible] A great deal of evidence has been furnished demonstrating hyperglycemia in *psoriasis*.[illegible] Traber was unable to confirm these findings. However there seems to be a relationship between diabetes and psoriasis which expresses itself in the occasional coincidence of both conditions in individuals and families. Greenwood[illegible] found 2.4 per cent of *psoriasis* among his 500 diabetics. This was ten times the percentage of the control group.

[illegible] Rost, G. A.: Hyperglycemia and Skin Diseases, Brit. J. Dermat. & Syph. 44: 5, 1932.
[illegible] Rosenfeld, G.: Hauttalg und Diät, Zbl. Ges. Med. No. 40, 1906.
[illegible] Schwartz, H. J., Highman, W. J., and Mahnkin, H. C.: Sugar Content of the Blood in Various Diseases of the Skin, J. Cutan. Dis. 34: 159-165, 1916.
[illegible] Kertész, G.: Dermatology in Diabetes, Dermatologica 87: 89-93, 1943.
[illegible] Strickler, A., and Adams, J. D.: Blood Sugar Metabolism in Certain Dermatoses, Especially in Acne Vulgaris, Arch. Dermat. & Syph. 26: 1-10, 1932.

CHAPTER XXIX

METABOLIC DISORDERS

Lipidoses

Chemical Data —The following lipids occur in the organism

1 *Sterols* This important group which includes cholesterol and its esters the bile acids the sex hormones and some other organic substances has a characteristic structure with four rings [2079] Cholesterol is absorbed and synthesized in the body It is excreted in the bile and partly reabsorbed the larger part being transformed into coprosterol and eliminated with the stools Cholesterol always accompanies neutral fat

2 Nitrogen and phosphorus-containing *phosphatides* such as lecithine cephalin sphingomyelin and the cerebrosides

3 The *neutral fats fatty acids* and *soaps* These form the bulk of the body fat

Normal (average) values for *lipids in the blood serum* [930]

	mg% Plasma		mg% Of total lipids
Total cholesterol	180	(110 150 Windaus) (100 210 Peters and Van Dyke)	34
Cholesterol esters	185	(40 70)	70
Lecithin	225		43
Total fatty acids	345	(190 420) (Peters and Van Dyke)	66
Total lipids	525	(700-800 Schaaf[1116]) (570-820 Peters and Van Dyke)	100

Three per cent of the net weight of normal skin is made up of lipids Five to fifteen per cent of the total lipids is cholesterol Lecithin varies from only a trace up to 30 per cent of the total lipids

The lipids in the serum depend on the intake and absorption the migration the deposition and disintegration of fat in the system and on the disturbances of the lipid metabolism in the cell [2079]

Pathology and Pathogenesis —Several disturbances of the fat metabolism are accompanied by tumor like lesions in the skin and in other organs which are called *xanthomas* While there are vast differences in the clinical appearance and in the severeness of the systemic involvement the histologic picture of all xanthomas is characterized by the presence of certain characteristic cells which are imbedded in a stroma

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2079 Thannhauser S J Lipidoses Oxford Medicine Vols IV VIIA New York 1940 Oxford University Press

930 Montgomery H and Osterberg A E Xanthomatosis Arch. Dermat & Syph. 37 373-402 1938

These cells, called foam cells, are large, at least of epithelium size. They occur mostly in nests, but diffuse infiltration to the degree of almost complete substitution of the normal tissue is known. The foam cells are constituents of the reticulo-endothelial system (Aschoff and his school, see Thannhauser[779]). Periadventitial reticulum and phagocytic connective tissue cells may become foam cells by being stuffed with fat droplets. In their mature stage they look alike. The foam cells may form giant cells of various types but there are no mitoses. Pigment, probably of blood origin, is frequently present. Cholesterol esters stain brown with Sudan III and dark blue with Nile blue sulfate. In polarized light they show the cross figures of double refraction.

The conceptions of the pathogenesis of the xanthomas and especially of the origin of the lipids in the foam cells have often changed.[1018, 2010, 2029, 2031] Pollitzer and Wile[2031] observed that the xanthomatous changes started in the adventitia of the small blood vessels. They concluded that the lipid substances in the xanthoma cells stemmed from extravasated blood and that their presence stimulated the connective tissue of the skin to hyperplastic growth. L. Pick and F. Pinkus,[2032] however, refuted the idea of hyperplasia or tumor formation. They suggested that the cholesterin infiltration of the cells was caused by the hypercholesterolemia which is often associated with xanthoma formation. However, xanthoma cases without hypercholesterolemia and the frequent hypercholesterolemia in diabetes, icterus, renal disease, and pregnancy without xanthoma formation made it probable that hypercholesterolemia was not the only source of the fat in the foam cells. Aschoff and his school (lit. see Thannhauser[779]) demonstrated that *only the cells of the reticulo-endothelial system could become xanthoma cells*. Another advance was the *chemical identification* of the lipid in the various forms of lipidoses with cholesterol dominating in the xanthomas.[2033] L. Pick[2033] interpreted xanthoma formation as a storage disease. The fat droplets which were taken up and stored like vital dyes by the cells of the reticulo-endothelial system apparently could not be disintegrated in the intermediary metabolism.

The decomposition of the blood lipids in the light of colloid chemistry is the center of the xanthoma theory of Bloch, Schaaf and Werner,[2034, 2035] propounded later especially by Schaaf.[1018]

These authors emphasized the importance of the *ratio of the lipid constituents* in the blood and in the tissues (free and bound cholesterol, phosphatides, true fats and perhaps other compounds as well). A change of the ratio of the lipid fractions would disturb the equilibrium of the lipid emulsion of the serum and lead to a coarsening of the lipid particles in the emulsion, to decomposition and

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[2031] Pollitzer, S., and Wile, U.: Xanthoma Tuberosum Multiplex, J. Cutan. Dis. 30: 235-241, 191[.]

[2032] Pick, L., and Pinkus, F.: Über doppeltbrechende Substanz in Hauttumoren etc., Monatschr. f. prakt. Dermat. 6: 46, 1908.

[2033] Pick, L.: Classification of Diseases of Lipoid Metabolism and Gaucher's Disease, Am. J. M. Sc. 185: 453-469, 1933.

[2034] Bloch, B.: Metabolism, Endocrine Glands and Skin Diseases, Special Reference to Acne Vulgaris and Xanthoma, Brit. J. Dermat. 43: 61, 1931.

[2035] Schaaf, F., and Werner, A. J.: Die Pathogenese der Xanthome: Die Beziehungen von Cholesterin, Phosphatiden und Gesamtfettgehalt des Blutes zur Entstehung der Xanthome, Arch. f. Derm. u. Syph. 162: 217-230, 1930.

precipitation of individual constituents in the tissues and finally to xanthomatous lesions It was suggested[1618] that the regulation of the concentration of fat emulsifying agents is a particular liver function the disturbance of which causes an impairment of the colloidal dispersion of fats in the blood serum and an increased tendency to throw the fats out of the emulsion Local contributory factors may modify the distribution of the xanthomas which develop in reaction to the deposits of de emulsified fats After formation of xanthomas the meta bolic disturbance may subside leaving the xanthomas In such cases xanthomas without symptoms of disturbed fat metabolism may be encountered

Schaaf s conception was based on Spranger s [2036] *investigations of emulsions* A fat in water emulsion is stable only if the concentrations of emulsifying agents are present in a definite ratio to each other Only under these optimal con ditions can the fat droplets remain in the finest possible state of dispersion Every variation in this ratio increases the readiness with which the fat separates from the water Cholesterol cholesterol esters and the phosphatides play an important role in the emul ification of fat in water In Ringer s solution con taining proteins in quantities corresponding to those in the blood serum optimal distribution of neutral fat in the pre ence of cholesterol and cholesterol esters takes place only if this mixture of emulsifying agents contains 60 per cent choles terol esters In normal blood serum 60 to 70 per cent of the total cholesterol is present in the form of cholesterol esters This fact stands in striking agreement with the optimal concentration of these two emulsifying agents

The ratio may also be changed by local factors such as trauma and inflam mation Schaaf s conception of xanthoma formation is further ba ed on the experimental production of xanthomas in animals Xanthoma formation in patients with a normal total fat content or a normal total cholesterol content is explained by the assumption of an abnormal ratio between the emulsifying agents especially cholesterol and cholesterol esters phosphatids neutral fats and fatty acids The absence of xanthomas in hyperlipemia or hypercholesterolemia can be explained by the stability of the colloidal system in spite of the total increase of lipids due to the correct ratio of the constituents

Montgomery [2037] recently reemphasized the old experience that cutaneous xanthomas are not uncommonly seen in association with *hepatic disease* espe cially obstructive jaundice (See Xanthomas)

Thannhauser and Magendantz[2007] and Thannhauser[2009] emphasized and proved again with a great array of evidence both chemical and clinical that the specific lipids which form the cellular deposits are only in some cases present in excessive amounts in the blood serum They claimed that there is no proof of a colloidal decomposition of the serum or of the cell fluids resulting in precipi tation which was the prerequisite of the hypothesis

They concluded that in one group of lipidoses which they called primary lipidoses the cause must be an intracellular disturbance of the lipid meta bolism The fat droplets in the cells are in their opinion not supplied by the

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[2036] Spranger W Zu physikalisch n Ch mi der Körperf tte Ein B itrag zu Physiologie d r Verfettung Bioch m Ztschr 208 164 178 10 9

[2037] Montgomery H Xanthomatosis J Invest Dermat 1 3 5-351 1938

blood stream but formed and retained within the cell in the presence or absence of hyperlipemia This theory found important support in the observation that *tissue cultures of xanthomas* are able to develop doubly refractile substances[2038] The primary lipoidoses are often hereditary Thannhauser and Magendantz[2007] did not deny that hyperlipemia may cause xanthomas Xanthomas in hyperlipemia of which the diabetic xanthoma is the best known type were grouped together as secondary or hyperlipemic xanthomatoses

Xanthomas

The cutaneous xanthomas are either solitary localized in a few areas or scattered over the body surface The solitary xanthoma is represented mainly by the eyelid xanthoma (xanthelasma) which is almost always flat (Xanthoma planum) Xanthomas in other regions are usually prominent either papular or tuberous (Xanthoma tuberosum multiplex) The xanthomas which are scattered over the body are mainly discrete shotty papules (Xanthoma disseminatum) which sometimes form large tuberous plaques

Xanthoma planum palpebrarum (often called **xanthelasma**) is the only common type of xanthoma All the others are rare conditions It forms a single or more often a small number of oblong soft flat hardly prominent light yellow plaques They surround the inner canthus in an arc which extends to the upper and lower lids Rare atypical lesions may be red brown or white hard or tuberous The author saw a case of xanthoma palpebrarum with tuberous nodules the size of a hazelnut so that the vision became disturbed

The lid xanthomas appear mostly in the fifth and sixth decades

The common and reputedly harmless but popularly and medically suspected xanthoma palpebrarum did not prove so insignificant as often believed Montgomery[2037] studied 38 cases More than 20 per cent had serious *cardiovascular disease* hypertension coronary sclerosis or angina pectoris There was a definite increase in one or more of the blood lipids[2039] and a consistent increase in lecithin Montgomery[2037] concluded that xanthoma palpebrarum is an accompaniment of systemic disease and that the condition is simply a variation of one of the types of xanthoma Polano[2040] found high or otherwise abnormal blood lipids in 25 per cent of the eyelid xanthomas Thannhauser and Magendantz[2007] call forme fruste of essential xanthomatosis a condition in which slight xanthoma of the lids dark pigmentation around the eyes and xanthosis of the skin due to carotenemia are the only (and inconstant) dermadromes However there is a *high blood cholesterol* and a *low basal metabolism* *Diabetes* and signs of angina pectoris are not infrequent findings The incidence of eyelid xanthomas in middle aged *lepers* (10 per cent) is more than ten times higher than normal It can be explained by high blood cholesterol and leprous involvement of the liver which is encountered in almost all necropsies

[2038] Biedermann W a I Hoefer I Züchtung von menschlichem Xanthomgewebe in vitro Arch f exper Zellforsch 10 93 1930

[2039] Curtis A C and Berger J P Effect of Feeding a Lipotropic Substance to Patients With Xanthelasma Arch Dermat & Syph 52 252 56 1945

[2040] Polano M I Die Xanthelasmatose der Haut Arch f Dermat u Syph 181 139-1 2 1940



Fig 264



Fig 265



Fig 266



Fig ˜6

Fig ˜64 — Xanthoma tuberosum multipl x Som disseminated papules (Courtesy Division of D matology D partment of Medici University of Chicago)

Figs ˜65-267 — Xanthoma (Courtesy Division of Dermatology D partment of Medicine University of Chicago)

Xanthoma Tuberosum Multiplex and Xanthoma Disseminatum.—A tendency to form lines, stripes or oblong arrangements is a peculiarity of both the xanthoma palpebrarum and the disseminated types.[2241] *Multiple xanthomas in small numbers (xanthoma tuberosum)* are typically localized on the extensor surfaces of the elbows, the knees and the heels. These xanthomas, except those of the palms, are rarely as flat as those of the eyelid. Papular, tuberous or lobulated forms on flat bases or short peduncles occur. The individual xanthomas may be crowded in ridges or furrowed plaques which may cover an entire axilla.[2241] The xanthomas in the neighborhood of joints and tendons may be very firm, originating in the tendons or tendon sheaths, and may become adherent to the bones. The variety of features and the transitional types show that a sharp anatomical distinction between localized and multiple and also between flat and tuberous xanthomas is not possible.



Fig. 68.—Xanthoma tuberosum multiplex. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Montgomery studied 26 cases of *xanthoma tuberosum*. High blood cholesterol, familial histories and early coronary (27 per cent) or other forms of severe vascular disease (46 per cent) were, *though not constant, surprisingly frequent* features. The combination of xanthoma tuberosum of the extensor surfaces with occlusive arterial disease is known since at least 1873 (Fugge after Thannhauser;[2079] also Barker[2204]).

2041 Wise, F., and Garb, J.: Xanthoma Diabeticorum With Unusual Form of Eruption, Arch. Dermat. & Syph. 45: 723-733, 1942.

2204 Barker, W.: Occlusive Arterial Disease of Lower Extremities Associated With Lipemia and Xanthoma Tuberosum, Ann. Int. Med. 12: 1891, 1939.

The rare *disseminate xanthoma* is characterized by an abundance of small papular, shotty lesions and plaques. This type favors the flexor surfaces but may involve the entire skin. Involvement of the scleræ and of the upper air passages occurs.



Fig 209 — Xanthoma tuberosum multiplex (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Herrmann and Nathan[2042] described very thoroughly (1926) two cases of xanthomatosis. In one case small xanthomas were disseminated over the whole body surface, and the blood cholesterol was normal. In the other case the

[2042] Herrmann, F., and Nath, F.: Zur Frage der Xanthomgenese, Arch f Dermat u Syph 151: 575-601, 1926.

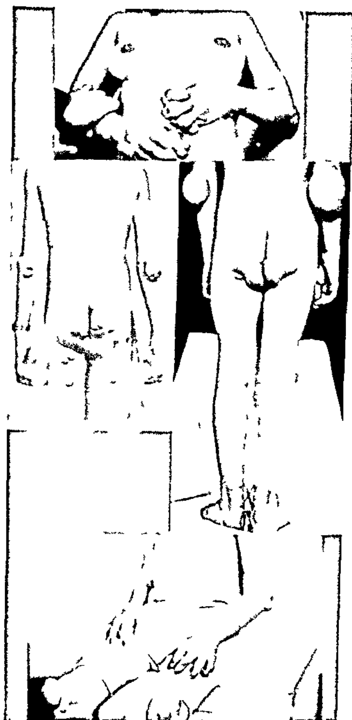


Fig 270 — Four sibling affected with tuberou xanthomatosis of the extensor type. Father who had high blood cholest rol married a second ou in Of ine children fl e were xanthomatous One of the other children suff red from car liac disease and had like anoth r non xanthomatous child high blood chol terol (From Bloom D Kaufma) S R and Ste n R A Arch D rmat & Syph 194)

xanthomas were tuberous and limited to the extensor surfaces of the knees and elbows to the extensor tendons of the fingers and to both Achilles tendons The blood cholesterol was high a brother of the patient had hypercholesterolemia without xanthomas The authors emphasized that the two cases represented *two clinically and pathogenetically different types of xanthomatosis*

More recently Polano [040] Thannhauser and Magendantz [2007] Montgomery and Osterberg [030] and other writers investigated the features of the two types Tuberous xanthomas of the extensor surfaces in moderate number appearing early in life, involvement of the tendons and tendon sheaths cardiovascular and liver disease high blood lipids and dominant heredity characterize one type Disseminate abundant small nodular xanthomas with predilection for the flexor surfaces involvement of the brain and nerve tissue causing diabetes in sipidus and invasion of the bones larynx lungs and lymph nodes feature the

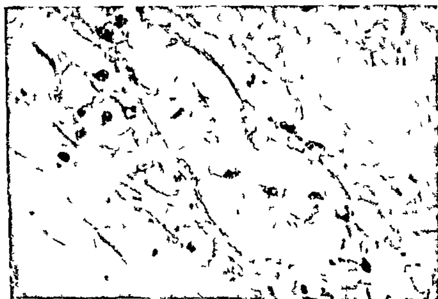


Fig 271 — Hereditary xanthomatosis Foam cells in a lipid deposit in the aorta (From Bloom D Kaufman S R Stevens R A Arch Dermat & Syph 194-)

other type There is no jaundice These cases of the disseminate type usually have *normal* or high normal blood cholesterol The prognosis is particularly bad if the air passages are involved which may necessitate tracheotomy Thannhauser and Magendantz [007] emphasize that they were not able to find a single case described in which disseminate xanthoma was found combined with endocardial and vascular xanthoma The situation is quite different in the extensor type The xanthomatous involvement of the endocardium the valves and the large vessels particularly the aorta is the cause of the sudden deaths which occur very strikingly in the xanthoma families The case of Arning is particularly well known The mother and five out of nine children had xanthomas Three of

the children died at the ages of 16, 21 and 26 years of sudden heart attacks, two of them while dancing. Similar dramatic fatalities have been reported repeatedly.[2044] The exhaustive necropsy findings in such a case have recently been published by Siegmund.[2045] A girl of six years had been showing xanthomata tuberosa of the extensor surfaces of the buttocks and of the eyelids since the age of six months. Gradually the girl grew weaker and died from circulatory collapse. The heart valves, the root of the aorta and the coronary arteries showed lemon yellow xanthomas with cholesterol and calcium deposits. There was central congestion and atrophy of the liver, but the Kupffer cells were free of fat. The kidneys showed xanthomas in the papillae. It is remarkable that the reticulo-endothelial system was free of fat. Two years later a brother 11 years old died suddenly. The post mortem findings were almost identical and so were those in one of the 5 stunted siblings in the case of Bloom, Kaufman and Stevens.[2044]

Liver disease was found connected with xanthoma as early as 1850 by Addison and Gull.[2046] Montgomery[2037] demonstrated hepatic disease, particularly obstructive jaundice, in 8 out of 55 xanthoma cases. Xanthomatosis in icterus following neoarsphenamine treatment has been seen in several instances.[2047, 2048] *Biliary cirrhosis is apt to be seen with cutaneous xanthomas of the flexor surfaces.* The cause of the obstructive jaundice is often found in xanthomatous changes of the bile ducts.[2049]

Hyperlipemia is present in tuberous xanthoma but the normal ratio between cholesterol and cholesterol esters frequently remains undisturbed. Its inversion proves severe liver damage.[1078] Phosphatides (lecithin) are likely to occur. In many cases of hepatic disease associated with cutaneous xanthoma in other locations than in the eyelid, *palmar* lesions can be found. The eyelid xanthomas in jaundiced patients often look lighter than the neighboring skin.

Cutaneous xanthomas may undergo involution as the condition of the liver improves. Thannhauser and Magendantz[907] point out that frequently the cause of the liver disease in tuberous xanthoma is a *xanthomatous biliary cirrhosis.* Enlarged liver and spleen with jaundice of years duration, hypercholesteremia with inverse ratio of cholesterol: cholesterol esters, together with xanthomata tuberosa and plana of the extensor surfaces and buttocks are a characteristic diagnostic triad. If xanthomas of the tendon sheaths and tuberous xanthomas of the skin exist over a long time without jaundice, involvement of the liver is rare.

In cases of biliary cirrhosis caused by xanthomatous involvement of the liver an *eruptive, universal, papulopustular form of xanthoma* was seen, which in con

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[2044] Bloom, D., Kaufman, S. R., and Stevens, R. A.: Hereditary Xanthomatosis. Familial Incidence of Xanthoma Tuberosum With Hypercholesteremia and Cardiovascular Involvement. Sudden Death in Several Cases. Arch. Dermat. & Syph. 45: 1-18, 1942.

[2045] Siegmund, H.: Kardiovasculäre Xanthomatose als Todesursache bei Jugendlichen. München. med. Wchnschr. 85: 1617-1619, 1938.

[2046] Addison and Gull: On a certain Affection of the Skin. Vitiligoidea (a) Plana, (b) Tuberosa. Guy's Hosp. Rep. 2nd Series vol. 7, p. 65, 1851.

[2047] Kulchar and Stoke: Multiple Xanthoma. Arch. Dermat. & Syph. 27: 157-348, 1933.

[2048] Nobl, G.: Formen der generalisierten Xanthomatose. Dermat. Wchnschr. 94: 877-883, 1932.

trast to xanthoma without liver involvement was extremely itchy The soft small papules were scratched so that a prurigo like picture resulted

The multiple forms have been encountered early in life in many cases in childhood Urbach emphasizes that in childhood the fresh papular lesions are often bright red and not yellow due to the more abundant vascularization of the infantile skin The xanthomas rarely heal spontaneously

Hand-Schuller-Christian's Disease is a syndrome related to the xantho matoses It is characterized by the triad defects in the flat bones of the skull exophthalmus and diabetes insipidus [049] Rowland [050] recognized the lesions of this disease as a special type of xanthomatosis with lipid storage in many parts of the reticulo endothelial system The infrequent involvement of the skin is surprising in this syndrome in view of the particular affinity for the skin in the other forms of xanthomatosis There are on record some cases with eczematous or purpuric yellow or red brown widespread papular rashes A few developed xanthomata palpebrarum and disseminata In one of the cases [051] the lenticular dermal xanthomas occurred in great profusion about the mouth and neck and the flexures of the big joints On the penis they were so numerous that a phimosis resulted Purpura may precede the xanthomas In the eczematous lesions of one case foam cells were found [0] Gottron[2051] interprets the Hand Schuller Christian dermatosis as a primary granulomatosis with econdary lipoid deposits in the later stages This clo ely follows the conception of Chester [053] who con sidered the granulomatous changes as the primary trouble and the lipid in filtration as secondary in the disorder Hypercholesterolemia has often been found

Secondary Xanthoma —(Xanthoma diabeticorum etc) Thannhauser and Magendantz[2007] emphasize that the eruptive form of xanthoma (xanthoma diabeticorum) is etiologically entirely different from all xanthomas due to primary xanthomatosis It is a symptom of lipemia and may occur in diabetic lipemia as well as in lipemia associated with other diseases It has been observed in cholesterolemia due to icterus pregnancy or nephritis The difference between primary and secondary xanthoma is well illustrated by the rare cases of combina tion of both In these cases the eruptive lesions disappeared under dietary treat ment but the tuberous primary xanthomata remained

The eruptive sub acute transitory and inflammatory character is the main distinguishing feature of the secondary xanthomas of which *xanthoma diabeti corum* is the best known (see diabetes)

Treatment of Lipidosis —According to Thannhauser and others the normocholesterolemic type does not respond to dietary treatment The case

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Christian H A D fects in Membranous Bo es Exophthalmus and Diabetes Insipidus Con tribution to Medical and Biological Res arch vol I New York 1919 Paul B Hoeber 1 c p 390

[050] Rowland R S Ch istian s Syndrom and Lipoid C ll Hyperpla ias of the Reticulo-Endothelial System A n Int Med 2 1 ... 1929 19 9

[2051] Gottron H Schüll r Ch istian Syndrome Arch f D rmat u Syph 182 601 731 191

[052] Wagn r R Di Spei herkrankh iten (Thesaurismosen) Erg bn d inn Med u Kinderh 52 56 193

[053] Chest W I ber Lipoi granulomatose Vi chows Ar h f path Anat 279 561-60 1930

associated with hypercholesterolemia may respond to a diet low in cholesterol Such a diet is mainly vegetarian no animal fats being permitted

Lipocaic is a defatted alcoholic pancreatic extract studied by L R Dragstedt It seems to contain a hormone which influences high lipid values in the blood and it should be tried in hypercholesterolemic xanthomatosis

Diabetic xanthoma responds quite readily to diet and insulin The diet should avoid too much fat particularly animal fat

A trial should be given to the treatment of xanthomatosis with ultraviolet rays The effects seem to be of a general nature exceeding the radiated area [2064] X ray treatment is locally effective in the tumors of Hand Schüller Christian s disease rarely in other xanthomas The eyelid xanthomas may be treated locally

A few very rare diseases which are interpreted as lipidoses may be mentioned briefly



Fig 27 Lipoidosis cutis et mucosae (lipid prot l osl) (Urbach Wi th) (Court sy Dr Erich Urbach

Extracellular-Cholesterinosis (Kerl-Urbach) —This is a chronic disease coming on over many years Maculopapular coalescent violaceous indistinct lesions and disseminated yellowish nodules are seen on the trunk In addition there are tuberous tumor like hard scaly larger nodules on the extensor surfaces of the arms and hands Some nodules appear on the soft palate

[2064]Rothmann St Xanthoma diabeticorum behandelt mit Quarzlicht Zbl 22 ?6 27 19 7

The fresh lesions are transparent papules with central vesicles Spontaneous involution occurs frequently The spleen is large and hard Serum cholesterol may be abnormal [2010] The lesions contained five times the cholesterol of the



Fig 273 —Lipoidosis cuti et mucosae (Urbach Wieth) (From Ramos e Silva J Arch Dermat & Syph, 1943)

normal skin Histological examination revealed an enormous extracellular lipid infiltration (mainly with cholesterol) and destruction of the elastic fibers Even the apparently normal skin showed lipid infiltration of the vascular walls Montgomery [2037] after describing a similar case does not feel that the recognition of a new entity is justified In contrast to Urbach s findings foam cells were present

X ray treatment was successful in a case of Frost and Anderson [2055]

[2055] Frost K and Anderson G R Extracellular Cholesterosis of Urbach Arch Dermat & Syph 39 1061 1939

Lipoidosis Cutis et Mucosae (Lipid Proteinosis) (Urbach-Wiethe).[2056] This condition has been shown to be a definite clinical and especially histological and histochemical entity.[2057 2058 2059] About thirty cases have been published showing a surprisingly uniform syndrome. The disease affects the skin and the mucosa in all the reported cases with nodular or hyperkeratotic lesions. Hoarseness in the first years of life is a characteristic early sign. A somewhat varioliform eruption appears during infancy and leaves irregularly outlined soft depressed scars. The hair growth is sparse. Later there is brown pigmentation and a scattering of yellowish very small papules on the face, the nape of the neck and the dorsa of the hands. The papules are not follicular.[2059]



Fig. 74. Lipoidosis cutis et mucosae (Urbach-Wiethe). (From Ramos e Silva, J.: Arch. Dermat. & Syph. 1943.)

Irregular scarry ridges and patchy depressions give the face a characteristic "knitted" appearance, at least in later years. Loss of the eyelashes, translucent nodules along the lids[2060] and indentations by scars add to the severe disfigurement. Especially in young persons some of the lesions bear crusts but there is no inflammatory border.[2059] The corners of the mouth show vertical grooves

[2056] Urbach, E., and Wiethe, C.: Lipoidosis cutis et mucosae, Virchows Arch. f. path. Anat. 223: 285-319, 1929.

[2057] Wise, F., and Rein, C. R.: "Lipoidosis cutis et mucosae" (Lipoid Proteinosis of Urbach), Arch. Dermat. & Syph. 37: ?01, 1938.

[2058] Sulzberger, M. B.: Case of Lipoidosis cutis et mucosae (Lipoid Proteinosis Urbach-Wiethe), Laryngoscope 52: 288-298, 194?.

[2059] Ramos e Silva, J.: Lipoid Proteinosis (Urbach-Wiethe), Arch. Dermat. & Syph. 47: 301-3?6, 1943.

[2060] Campbell, A.: Lipoid proteinosis (Urbach-Wiethe), U. S. Nav. M. Bull. 42: 669-675, 1944.

There are elevated firm elastic brownish yellowish white or flesh colored tumors on the extensor surfaces of the elbows and on the dorsal and lateral surfaces of the fingers They are crowded together in warty mulberry like rough plaques

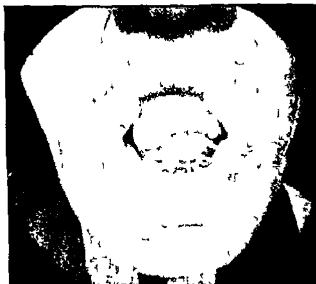


Fig 275 —Lipoidosis cutis et mucosae (lipoid proteinosis) (Urbach Wiethe) Yellow nodular lesion beneath the tongue and infiltration of lower lip (From Wile U J and Snow J S Arch Dermat & Syph 1941)



Fig 276 Lipoidosis cutis et mucosae (lipoid proteinosis) (Urbach Wiethe) Numerous pearly white papules along the margin of the eyelid (From Wile U J and Snow J S Arch Dermat & Syph 1941)

In some cases the papules undergo early involution persisting only on the elbows the knees and the hands The lips show on their inner surfaces fairly firm yellowish white plaques Similar plaques and streaks occur on the palate in the pharynx and on the under surface of the tongue which is rigid and limited

in its motion by a deep seated infiltration and thickening of the frenulum The papillae are mostly lost[2061] Similar thickenings symmetrically involve the tonsils and the larynx

In the majority of the cases either glycosuria or latent diabetes is present Heredity seems to play an important role Consanguinity of the parents and familial occurrences are on record Congenital hoarseness and developmental defects have also been observed

Laryngotomy because of severe dyspnea from scarring has become necessary in several cases

There can be no doubt that this is a characteristic syndrome The outstanding histological features in both the skin and in the mucosa are (Wise and Rein[2057]) an infiltration with a lipoid substance surrounding the vascular walls with massive deposits and vacuolization of the infiltrating masses seen in paraffin sections Foam cells and double refraction indicating cholesterol esters are absent The infiltration consists of a lipid probably bound to a protein

Burger and Grut[2062] described a severe lipidosis with extremely high lipemia hepato splenomegaly and a chronic *eruption* of small yellow elevated nodules on the extensor aspects and the buttocks The lesions mainly contained phosphatides but no foam cells and no doubly refractile lipids[2010]

Gaucher s Disease is a slowly progressive often hereditary chronic lipidosis involving the spleen the liver and the bone marrow An uneven brownish tan pigmentation especially on the parts is usually noticeable Chloasma like often symmetric patches as well as streaky patterns have been seen[2079, 2063] Such symmetrical pigmentations may form quite characteristic leaden gray reticular gross patterns on the lower legs dotted with more intensely pigmented spots In advanced cases the skin of the pigmented areas of the legs is glossy and scaly sometimes ulcerated These pigmentations leave the soles heels and toes free but they involve the instep areas in a sharply outlined spat like fashion[2063] There is a striking free margin just below the ankle Leg ulcers without varicose veins occur The mucous membranes may be pigmented but this is supposed to occur only if the adrenals are affected by the lipid deposits The pigment is melanin Brownish yellow triangular conjunctival thickenings occupying the interpalpebral space on both sides of the cornea but leaving a thin white stripe around the cornea appear slowly in the second decade These pingueculae together with bone changes and splenomegaly establish the diagnosis[2079] Purpuric tendencies occur at times[887] The specific lipid of Gaucher s disease which fills the large Gaucher cells in the involved organs is kerasin

Niemann Pick s Disease is another rare familial splenomegalic lipoidosis characterized by enormous accumulations of the diaminophosphatide sphingomyelin in the entire reticuloendothelial system The disease is fatal within the

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[2061] Szodoray L Lipoid Proteinosis (Urbach Wiethe) Dermatologica 83 375-386 1941
[2062] Bürger M and Grütz O Ueber hepatosplenomegale Lipoidose mit xanthomatösen Veränderungen in Haut und Schleimhaut Arch f Dermat u Syph 166 54 575 1932
[2063] Bloem T F Groen J and Postma C Gaucher s Disease Quart J Med 5 517-527 1936

first two years of life The skin[20 9 2064] of the infants is described as wrinkled pale and profusely sweating The subcutaneous fat disappears entirely The exposed parts and also the mucous membranes are diffusely pigmented and pigmented patches also occur in the mouth The pigment is melanin and possibly due to adrenal involvement [029 2064]

[2064]Pick L Niemann Pick s Disease and Other Forms of So-called Xanthomato s Am J M Sc 185 601-616 1933

CHAPTER XXX

METABOLIC DISORDERS

Hemochromatosis

Hemochromatosis,[2065] *pigmentary cirrhosis in diabetes* and *bronzed diabetes* are terms mostly used to designate a disease characterized by the production of pigment in almost all organs, diabetes in 78 per cent of the cases, and hepatic cirrhosis. The disease occurs almost exclusively (95 per cent[2066]) in men, mostly in the decade from 45 to 55 years. The disease was encountered five times among 100,000 hospital admissions.[2067] The onset is insidious with the symptoms of diabetes, with abdominal pain or pigmentation of the skin.

The course depends on the diabetes and the cirrhosis. Before the advent of insulin about fifty per cent of the patients died in diabetic coma. Today the prognosis seems better since the outcome mainly depends on the course of the cirrhosis, which may be protracted.[2068] *Primary cancer of the liver occurs in* 7 per cent.[2066]

No specific treatment is known and though insulin may lengthen life the disease is ultimately fatal.

The striking pathological feature is the abundant production of pigment which is deposited in almost all organs though in varying amounts. The most heavily affected organs are the liver, the pancreas, the adrenal, the salivary glands and the lymphatic nodes. There are two pigments present. *Hemosiderin* gives the iron reaction and *hemofuscin*[2065] is an iron free melanin. The iron content of the organs which have been mentioned as the sites of the main deposits may be a hundred times higher than normal.

The etiology is not known. Familial occurrence has been observed.[2069] Sheldon, who has reviewed 345 cases in a comprehensive monograph, classes hemochromatosis as an *inborn error of metabolism* concerning the cells which later in life begin the cirrhosis of the liver and of the pancreas.

Dermadromes. The skin participates in the general process of *pigmentation though not nearly as much as the liver and the pancreas.* Discoloration is absent in only one sixth of the cases. The melanoderma develops insidiously and is the initial complaint[11-3] in about one fourth of all instances.[2066] It may precede the diabetic and hepatic symptoms by many years.[2070] It is more

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[2065]von Recklinghausen, F.: Hemochromatose, Versammlung Deutscher Naturforscher u. *Aerzte Heidelberg 1890, Verh. d. Ges. Naturforsch.* p. 324, 1889.

[2066]Sheldon, J. H.: Haemochromatosis, London, 1935, Oxford University Press.

[2067]Cain, J. C.: Hemochromatosis, 6 Cases, Texas State J. Med. 36: 3 6-303, 1940.

[2068]Butt, H. R., and Wilder, R. M.: Hemochromatosis: A Report of Thirty Cases Diagnosed During Life, Proc. Staff Meet. Mayo Clin. 12: 6 6 7, 1937.

[2069]Lawrence, R. D.: Hemochromatosis and Heredity, Lancet 2: 10 5, 1935.

[2070]Becker, S. W., Shamburg: Disease Associated With Hemochromatosis, Arch. Dermat. & Syph. 24: 380-382, 1931.

often diffuse than patchy or freckled In many instances the pigmentation covers the entire body but it is more pronounced in the parts exposed to the light and in the axillae the nipples the umbilicus and the genital region As in Addison s disease scars may become heavily pigmented

The *color* varies considerably [2066] In about twenty per cent of the cases the color is described as bronze ranging from a light bronzing to deep brown and even black An equal group is characterized by the presence of a gray slate or bluish hue with a metallic reflection The face tends to acquire a metallic sheen more readily than the body which usually remains brownish The *metallic component* is more often seen in advanced cases The oral *mucosa* particularly of the cheeks is often pigmented The discoloration is more spotty than diffuse being brown or slate The lips and conjunctivae may also become pigmented

Except for the pigmentation the skin is not much changed Dryness scaliness and pruritus may be troublesome [2071] *Purpura* occurs in about fifteen per cent [207]

Of great interest are the symptoms which indicate *endocrine* influences They include atrophy of the testes and prostate impotence loss of axillary and pubic hair and thinning of the beard eyebrows and chest hair [2073]

The pigmentation of the nipples and of the genitalia must be interpreted in the same way Deficiency of urinary androgen and of adrenal cortical hormone has also been found These endocrine features seem to be accompaniments of the hepatic cirrhosis which is such an important part of the syndrome (see hepatic cirrhosis)

The pigmentation increases with the progress of the disease Improvement has only rarely been reported most often in connection with insulin treatment [068]

As is the ca e in other organs the skin pigment is composed of hemosiderin and hemofuscin The hemosiderin appears microscopically in fine granulas most densely accumulated in the membranae propriae of the sweat glands and in the vascular endothelium while the hemofuscin appears in coarse deposits in the epidermis and in the corium The ratio of the two pigments varies [1316] In some cases the hemofuscin is entirely absent (Roth after Kaufmann[11 5])

An *iron reaction in the living* skin has been devised by Fishback [2074] Intra dermal injection of a mixture of equal parts of 0 5 per cent potassium ferrocyanide and one hundredth normal HCl produces a wheal which turns deep blue in the pre ence of iron after five minutes

Diagnosis see Table I

Alkaptonuria and Ochronosis

A rare hereditary metabolic disorder in which the oxidation of the amino-acids tyrosin and phenylalanin is disturbed is called *alkaptonuria* The urine

[2071] Walther Pigm cirrhos (Bronzediabetes) 211 39 131

[2072] Stetson R P and F rris H W Hemochrom tosis and Purpura Arch. Int Med. 50 23 239 1932

[2073] Labbé M Boulin R and Uh y P Diab te b o zé avec atrophie des organs génitaux et chute des poils (syndrome hépato-pancreato-génital) Bull t mém. Soc méd d hôp de Paris 50 15 4 1577 1934

[2074] Fishback H R Clinical D monstration of Iron in Ski J Lab & Clin Med. 25 98-99 1939

darkens on exposure to the air because of its content of homogentisic acid This formation of pigment is closely related to the formation of melanin under normal and pathological conditions After a long duration of alkaptonuria a dark iron free pigment melanin like in character[11 5] is deposited in the connective tissues predominantly in the tendons and cartilages Virchow called this condition *ochronosis* The ochronotic tissues cause characteristic surface dis



Fig [illegible] 7 Ochronosis Dark colored spot in ear At right ear in transillumination Note dark cartilages (From Smith J W J A M A)



Fig [illegible] 8 Ochronosis Slate colored spots indicating the insertion of the tendons of the musculi recti

colorations wherever they are superficially enough situated This is the case in the sclerotics where slate colored or even black scleral spots appear on both sides of the cornea but separated from the limbus corneae by a narrow white strip Thus *4 triangular figures* with dark centers result Obviously the site of these spots denotes the underlying insertion of the tendons of the rectus muscles The influence of light may enhance the pigment formation

Slit lamp microscopy reveals deposits of pigment in the *cornea*[2075]. Other, though less frequent and conspicuous gray, greenish or even black discolorations are seen in the *ear*, particularly the anthelix and concha, the tip of the nose and in the upper eyelids. Transillumination of the ears makes the cartilages visible as dark shadows[2076]. The ear ducts and the nasal septum may also be discolored. The cerumen may be black[2077] and homogenisic acid has been found in it.

Diffuse pigmentation of the face, sometimes to the degree of bronzing, bluish discoloration of the knuckles, the palmar eminences and the contact surfaces of the fingers have been observed[1125, 2077, 2078].

The *prognosis* depends on the development of destructive arthritis which occurs in the later stages.

Chronic *phenol poisoning* from prolonged wet dressings with 1 — 3 per cent carbolic acid may produce the same changes as spontaneous ochronosis.

The *morbid anatomy* in fully developed cases is dominated by the black discoloration of the entire cartilage system.

A low protein diet is advised in the management of ochronosis[85].

Hyperuricemia—Gout

Purine substances are ingested mainly with liver and other viscera, fish eggs and other foods rich in nucleoprotein. A certain amount is synthesized in the body. The end product of purine metabolism in the human organism is *uric acid* which is excreted in the urine mostly as urates.

Gout is an unexplained disorder of the purine metabolism. The values of the normal as well as the gouty uric acid level in the blood vary remarkably. Figures over 2.5 mg per cent[2079], over 4.5 — 6 mg per cent[12, 2080, 2081] and over 8.5 — 9.5 mg per cent are samples of what is considered *hyperuricemia* by various authors. Deposits of urates in various tissues, especially in and around joints[2082, 2083] are a characteristic feature. Heredity seems to play a part[2084]. Ninety five per cent of the gout patients are *males*. About 5 to 8 per cent of the patients with joint disease have gout[85, 2085]. It is still—as in Sydenham's time—[2086]

[2075] Smith J W Ochronosis of Sclera and Cornea Complicating Alkaptonuria Review of Literature and Report of 4 Cases J A M A 120 1 8 1282 1942

[2076] Swirsky M Y Ochronosis—Case With Alkaptonuria and Melanuria Clinic 2 1323 1333 1944

[2077] Poulson V Ueber Ochronose bei Menschen und Tieren Beitr z path Anat u z allg Path 48 346 1910

[2078] Pick L Ochronose Berl klin Wchnschr pp 478 509 5 6 531 1906

[2079] Kinell J and Halsen R L Gout Review of 62 Cases M Clin North America 24 429–441 1940

[2080] Talbott J H Gout New York 1943 Oxford University Press

[2081] McCracken J H 50 Cases of Gout Bull New England M Center 3 249 251 1941

[2082] Hench P S Gout in U S A Proc Staff Meet Mayo Clin 12 6 69 1937

[2083] Hench P S Diagnosis and Treatment of Gout and Gouty Arthritis J A M A 116 453 1941

[2084] Bauer W and Klemperer F Medical Progress in Gout New England J Med 231 681-685 1944

[2085] Hench P S The Diagnosis of Gout and Gouty Arthritis Proc Staff Meet Mayo Clin 11 476-480 1936

[2086] Sydenham Th The Works of Thomas Sydenham vol 2 London 1850 Sydenham Society pp 123 16

Fig 279





Fig 280

Fig 279 — Gout dormant tophu
Fig 280 — Gout

to some extent true that a higher social status (arthritis divicium of the old physicians) predisposes to gout [2087, 2088] Though manual work and poverty do by no means protect against the trouble Most writers agree that overindulgence in certain foods as is common in the holiday season may precipitate an acute attack[2089] in a gouty person

The clinical picture of gout is dominated by repeated acute and extremely painful attacks of arthritis mostly in the small joints Involvement of one big toe (podagra) is a frequent event In spite of the acute inflammation there is no suppuration and complete restoration to normal function is the rule The urinary excretion of urates is subnormal before and in the initial phase but increases rapidly during the attack

In the chronic stage the attacks occur more frequently and last longer More and also bigger joints become affected and urate deposits deform and destroy the articular cartilages *Tophi* as the demonstrable deposits of urates are called often appear in the neighborhood of joints in and around tendons in the ears and occasionally in the subcutis

Kidney function is often disturbed The progno is depends on the amount of articular damage renal complications and the degree of cooperation by the patient in avoiding such foods which are prone to cause attacks Colchicine relieves the acute attack and cinchophen improves the output of uric acid in the interval although many con ider it too toxic Salicylates are widely used as a less dangerous substitute Hench [08] calls the therapy of gout which has not advanced since the advent of cinchophen a reflection on medical progress

Dermadromes—The ruddy complexion and obesity[2079] of the typical gouty man are often mentioned Sydenham spoke of his thick shaggy eyebrows and his full crown of hair [2090] The older literature emphasized and probably overrated the importance of gout in the etiology of dermatoses Today to a large extent due to the skeptical attitude of J Jadassohn (1905) who called the evidence scanty and uncertain the only recognized skin manifestation of gout is the tophus of the skin The tophi are rarely present before or during the first attacks but they are almost invariably seen in chronic gouty arthritis [2085] Tophi in connection with the skin are seen in about one third of the cases about the small joints and on the ears They are often found on the lateral aspects of the fingers but also about the elbows knees and heels On the *ears* where they occur in the vast majority of the cases of tophaceous gout [2081, 087] they most frequently occupy the helix The tophi are nontender very firm nodules of varying movability The size varies from a few millimeters to one centimeter in diameter but they are occasionally much larger The color of the skin over superficial tophi is pale yellow The nodules may ulcerate and in the contents microscopic needle shaped crystals of sodium urate may be found [1, 6, 2091]

[2087] McCracken J P Owen Ph S and Pratt J H Gout Still a Forgotten Diseas J A M A 131 367-372 1946

[2088] Brachn r Mortens n K 100 Gouty P ti nts Acta med Scandinav 106 81 107 1941

[2089] Rutledge D J a d Bedard R E Crite ia for the Diagnosi of Presumptiv (Pr tophaceou) Gout Managem nt of an Illu trati e Cas Proc St ff Meet Mayo Clin 12 140 156 1937

[2090] Lichtwitz L Gout Bull New York Acad Med 10 306-319 1934

[2091] Chri toph r F and Monroe S E Tophi of Heel J A M A 110 -149 1938

The diagnostic value of typical tophi is great. Many clinicians have stressed looking at the ears in all cases of painful arthritis.

Pruritus is a frequent symptom of gout.[12] W. N. Goldsmith[2090] calls gout the most frequent cause of itching, which certainly is not true in the U.S.A. Pruriginous eruptions, urticaria and papular and bullous lesions have occasionally been seen, paralleling the level of the hyperuricemia.[2092] Sheaves of urate crystals were found in the lesions in some cases of papules and nodules of the skin of the lower legs.[2093] The same is true of psoriasis,[2094] erythromelalgia[2095] and especially of eczema. Kromayer,[2096] the last to report a large series of gouty eczema, saw its criteria in obstinacy, recurrence in the same spot, location in unusual places not subject to external irritation, multiplicity of patches and the coexistence of various arthritic and neuritic complaints. Unfortunately his diagnosis and definition of gout are not up to the present standards, but one should not dismiss lightly his impressions nor those of other experienced clinicians. Garrod (after Bulkley[19]) found that 47 per cent of 2000 patients with gout had eczema. Bulkley[19] considered fully 30 per cent of his eczema patients as gouty.[12, 1133]

Despite these impressive figures the relationship of gout and eczema remains controversial. *It is now generally considered of small importance.*

The *blood uric acid in eczema*—and for that matter also in pruritus, psoriasis and urticaria—varies with a tendency to increased levels, especially in severe cases.[12] There is good reason to assume that in some of these cases the inflammatory and destructive processes in the skin are likely to be the cause of the hyperuricemia rather than its sequel.[2097] Injections of uric acid into the blood of patients with eczema have been shown not to influence the skin lesions.[2098]

Symmetric hyperkeratosis *of the hands and soles, together with erythema* of the palmar eminences has been seen in several cases of hyperuricemia.[2099] This condition occurs alone and also together with several internal disorders, e.g., hepatic disease, the menopause and pregnancy, so that no specific significance can be attached to the dermatosis. Many observations, mostly older than twenty years, are concerned with the role of hyperuricemia in psoriasis. Zorn[2094] found that the scales in psoriasis contain a hundred times the amount of uric acid in the blood. He advises a purine free diet in eruptive psoriasis.

Tommasi and collaborators[100] have described an *alopecia* of the anterolateral aspects of the *lower legs* about corresponding to the area supplied by the

[2092] Comel, M.: Prurigo uratica. Gior. ital. di dermat. e sif. 78: 1093, 1939.

[2093] Richter, W.: Harnsaure Diathese in Verbindung mit Hautkrankheiten. Dermat. Wchnschr. 101: 1167, 1935.

[2094] Zorn, B.: Uric acid, Psoriasis and Gout. Dermat. Wchnschr. 96: 621, 8. 5. 1933.

[2095] Mackel, J.: Erythromelalgia Associated With Chronic Gout. Arch. Dermat. & Syph. 38: 73-74, 1938.

[2096] Kromayer, E.: Ekzem und harnsaure Diathese. Deutsch. med. Wchnschr. 51: 15. 7. 15. 8. 19. 5.

[2097] Stümpke, G. and Bolka, G.: Blochemische Untersuchungen bei Hautkrankheiten. Med. Klinik 20: 1007-1012, 19. 4.

[2098] Schultz, J. C. and Nicholas, H. O.: The Behavior of Injected Uric Acid in Patients With Eczema. Arch. Dermat. & Syph. 14: 308-313, 19. 6.

[2099] Barber, H. W.: Gout: Volar Involvement. Proc. Roy. Soc. Med. 31: 701, 1938; also 26: 497, 1933.

[2100] Thommasi, L.: Alopecia of Personal Regions as Constitutional Sign of Neuro-arthritic Diathesis. Brit. J. Dermat. 52: 1. 9. 1910.

peroneal nerves together with slight atrophy of the skin and common baldness These easily detectable hairless patches are supposedly suggestive of a high blood uric acid level

Calcinosis of the Skin

It is difficult to characterize the internal disorder whose skin manifestations represent the various forms of cutaneous calcium deposits



Fig 281 —Calcinosis cutis (Courtesy Division of Dermatology Department of Medicine University of Chicago)

An exception is the metastatic calcinosis in which *calcium* deposits in the skin (striae) and other organs can be related to destructive *bone* disease e g osteomyelitis[2101] or myelogenous leukemia (Wels after Sutton *and* Sutton[447])

The term *chalk gout* (Minkowski after Steinitz[2102]) is based *on* the similarity of nodular calcium deposits about small joints to the *tophi of* true gout It is misleading in so far as an analogy to the uric acid metabo*lism in* gout is not sufficiently apparent in the calcium metabolism in calcinosis

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[2101] Jadassohn J Ueber Kalkmetastasen in der Haut Arch f Dermat 100 317 1910

[2102] Steinitz H Calcinosis circumscripta und Calcinosis universalis Ergebn d inn Med u Kinderh 35 216-275 1931

Cutaneous calcinosis occurs in two quite different types (Verse after Steinitz[2102]) with relatively few transitional forms. In the so called chalk gout or *calcinosis circumscripta* the calcium deposits appear as circumscribed nodules mostly about the terminal phalanges of the fingers and on the extensor aspects of the elbows. *The volar surface of the finger tips is often the first location*.[2103] The legs are rarely affected except for the patellar areas. The size of the nodules ranges from mustard seed to pea or even walnut size. Multiple deposits may simulate shots in the X ray picture. The nodules are usually nontender. Acute painful inflammations of the para articular tissues resembling gout may occur but they leave the joints and bones free.[2104]

Superficial nodules may ulcerate and extrude calcareous material. The mouth of such sinuses is often surrounded by a hard yellow ring.[2103] The nodules may become raised globular tumors[104] or the covering skin may be depressed and atrophic.

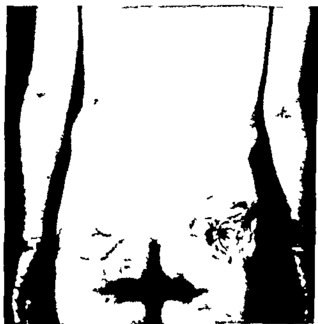


Fig 28. Localized calcinosis with scarring and sinus formation. (Courtesy Dr G Cooper.)

On the whole chalk gout in itself is not a severe disorder. The nodules may disappear spontaneously.[105, 2106] Life is rarely in danger. However 40 per cent of the cases[2107] are combined with scleroderma, Raynaud's disease and acrodermatitis atrophicans.

[2103] Epstein E. Idiopathic Calcinosis Cutis. Arch Dermat & Syph 34 367-377 1936.
[2104] Maloney E. R. and Bloom D. Cutaneous Calcinosis. Arch Dermat & Syph 23 245 1931.
[2105] Swanson W. W., Forster W. G. and Iob V. Calcinosis Circumscripta. Am J Dis Child 45 590-593 1933.
[2106] Weber F. P. Improvement in Cases of Calcinosis Universalis in Children. Brit J Dermat 47 400-401 1935.
[2107] Atkinson F. R. B. and Weber F. P. Cutaneous and Subcutaneous Calcinosis. Brit J Dermat 50 267-310 1938.

The female patients with chalk gout outnumber the males about 6 to 1 The disease occurs most often in persons beyond the thirty fifth year of life and the onset has repeatedly been seen connected with the menopause [2108-2110] It appears rarely in the young [2105 2111] at lactation or at puberty [2112] Familial occurrence is known [2113]

In the *diffuse* variety of calcinosis known as *calcinosis universalis* any part of the skin may become affected though there is a tendency to involve the neighborhood of the big joints Symmetry is a feature and a decrease in the number of deposits towards the acra is often apparent



Fig 583 —Male aged 83 years Large subcutaneous calcareous plaque existing for many years Secondary infection and sinus formation

The lesions develop in crops with fever and general reactions The course is progressive so that finally almost the entire skin may become involved Large calcareous plaques in or under the skin may form and ulcerate Deeper structures may become affected and a septic syndrome with fever immobility of muscles multiple chalk abscesses and cachexia may result The evacuation of large chalk abscesses may improve the picture In some cases several quarts of chalky matter could be drained from huge cold abscesses [21] In chronic

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[2108] Stran l ll Birg r and Hess Iman B H Ein Fall von Kalkgicht Hygiea 91 686-694 1932 Zbl 43 467

[21] I ntoppi la B Subcuta K lkknot n bei pluriglanduls r Insuffizi nz Hospitalistid 64 1 13 19 1 7l l 2 41

[2] Cubrau H B itrag zur F age d r Kalkansammlung i in d r Haut D rmat Wchnschr 80 113 116 19

[111] Jacobowitz H Ein besond re Ve lauf form bei Cal inosi universalis Zschr f Kind rh 53 597-601 193

[2 12] Ce lards I Ueber K lkgicht Fall Diss 1931 Marburg a. d L.

[2 1] Weis b h R J François F and Robert P Calcificati ns souscutanees et arthrite s che Paris méd 1932 II 8 3

cases a combination of sinuses scars and ulcerations creates a picture which resembles scrofuloderma The prognosis is generally unfavorable[2114] though long remissions and occasional cures have been observed Combination with scleroderma has been seen in 32 per cent of the cases of calcinosis universalis [2107] The disease is more frequently encountered in young persons and children[2115] than in middle or advanced age [2102]

Rosenberg [2116] Brooks[2117] and other writers who recently reviewed the subject feel that neither the theory of the deposition of calcium due to a disturbed calcium metabolism in analogy to uric acid in gout nor the theory based on the assumption of the deposition of calcium in already damaged tissues [2118-2119] have been convincingly proved *The bony skeleton is usually intact and the blood* chemistry has been found normal [2120] Experimental hypercalcemia did not in the work of most of the experimenters lead to deposits [2121] Except in scleroderma which accompanies only about 40 per cent of all the cases of calcinosis preexisting degeneration or necrosis has not been discovered In these cases the calcium metabolism is often disturbed

No specific treatment is known Abscesses should be drained since general improvement has occasionally followed A diet low in calcium seems sensible None of the many procedures which have been tried on theoretical grounds [2107] has been confirmed or accepted

Hypocalcinosis has been seen associated with impetigo herpetiformis and pustular psoriasis (See chapter Parathyroids)

Amyloidosis

Amyloid is a protein which may occur in the skin [2122] in a primary dermatosis (lichen amyloidosus) in the course of other especially senile dermatoses [2123] or in certain tumors Much rarer is cutaneous amyloidosis as part of the generalized amyloidosis which develops in chronic cachexias especially tuberculosis Cutaneous nodules[2124] and erythemato—pigmentary or erythromelalgic changes[2125] have occasionally been recorded but they seem to be very rare Also very rare

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[2114] Rémy Rou Sur un cas de granulations calcaires sous-cutanées Bull et mém Soc de radiol méd d Fra ce 20 437-440 193 Zbl 43 554

[2115] Hungerlan I H Calcinosis universalis bei einem Kinde Zbl 54 [illegible] 1936-1937

[2116] Rosenberg E F Chalk Gout J A M A 115 1 91 1794 1940

[2117] Brooks W D W Calcinosis Quart J Med 3 [illegible]93-319 1934

[2118] Than haus r S J Lehrbuch des Stoff echsels un I d r Stoffwech elkrankheite i München 19 9 J F Bergmann p 603

[2119] Bil rt Hag mann F Di Calcinos n d r Haut under B rücksichtigu g zweier Fälle von Acrocal inos Di s 1932 Hamburg

[2120] Friedländ r J Untersuchungen des Gesamtmineralwech els bei Calci osis universalis Deutches Arch f klin Med 166 10[illegible] 121 1930

[2121] Gougerot and Cart au I Contribution à la pathogénie d s gra ulomes calcaires Absence de réactions inflammatoires Résorption des s ls calcaires injectés loin des lé ions et dan les lé ion Bull Soc franç de d rmat et syph 39 701 704 1932

[2122] Sa nicandro G La d generazion amiloide della cut Gior ital di dermat e sif 74 1499-1534 1933

[2123] F eudenthal W Amyloid in der Haut Arch f D mat u Syph 162 40-94 1930

[2124] Michelson H E and Lynch F W Systematized Amyloidosi of the Skin and Muscles Arch Dermat & Syph 29 805 8 0 1934

[2125] Fies inger N Fauvet J and Albaharry Cl Un cas d amylose hépatique et cutanée Bull et mém Soc méd d hôp de Paris 58 274 275 1942

is a peculiar form of *systemic amyloidosis* which not only produces an unusual dermatosis, but follows a different pattern in the distribution of the amyloid avoiding the spleen and the large glands which in the typical cases contain the largest deposits of amyloid Instead the smooth and the striated muscles



Fig 284



Fig 285

Fig 284 —Localized amyloidosis (Courtesy Division of Dermatology Department of Medicine University of Chicago)

Fig 285 —Amyloidosis cutis (lichen amyloidicu) (Courtesy Dr H E Kittredge)

including the heart are the site of widespread amyloidosis [2126-2128] Enlargement fissuring and nodularity of the *tongue* was present in all cases There may be difficulty in closing the mouth and the *gait* may be shuffling The clinical aspect of the skin in some of the cases[2127, 2129, 2130] is characterized by *transparent* or yellow waxy small high firm papules which cover some areas very densely

[2126] Lubarsch O Zur Kenntnis ungewöhnlicher Amyloidablagerung n Virchows Arch f path Anat 271 867 880 1929

[2127] Königstein H Amyloid der Haut Handb d H u Gk 4 3 254-357 1932

[2128] O Leary P A Montgomery H and Brunsting L A Systematized Amyloidosis of the Skin and Mucous Membranes Bence-Jones Proteinuria Arch Dermat & Syph 31 408-409 1935

[2129] Bosellini P L Sopra I amiloidosi cutanea Česká Dermat pp 57-62 1931 Zbl 41 470

[2130] Mollow W Zur Klinik der systematisierten Amyloidose Verhandl d deutsch Gesellsch f inn Med pp 555-559 1930

The eyelids, scalp, the pubic and adjoining areas, the palms, the dorsa of the feet and other sites have been seen covered with the lesions, which at first glance because of their transparency give the impression of vesicles. Atrophy, telangiectases and purpuric spots are other features. In some cases the lesions were very firm large nodules [131, 132] or large sclerodermatic plaques.[134]

All the patients were middle aged or older.[134] Multiple myelomas and Bence Jones proteinuria have been found in some cases.[134]

The presence of amyloid in the living skin can be demonstrated by the subcutaneous injection of 0.1 per cent solution of congo red in saline. The produced red spot fades within 4 days in normal skin, but remains visible up to 12 days if amyloid is present at the site of injection.[135, 136]

The amyloid forms a band in the upper cutis, the epidermis being atrophic and free of amyloid. The vascular walls and the muscles contain large deposits. The spleen and the large glands have no amyloid or only along the blood vessels.

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[131] Gottron, H.: Kreislaufstörungen und Hämorrhagien der Haut. In: Arzt and Zieler's Die Haut und Geschlechtskrankheiten, vol. II, Berlin 1935, Urban & Schwarzenberg, pp. 23-?

[132] Gottron, H.: Grossknotige ... Erscheinungsbild einer ... Amyloidose der Haut. Zbl. Haut. 57: 1937-1938.

[133] Matras, A.: Amyloidose der Haut. Zbl. 51: 4-6, 1936-193?

[134] Gottron, H.: Systematisierte Haut-Muskel-Amyloidose unter dem Bild ... Sclerodermaamyloidosum. Arch. f. Dermat. u. Syph. 166: 584-615, 193?

[135] Marchionini, A., and John, F.: Über ... und ... Hautamyloidose. Praktisch Diagnostik ... Hautamyloid ... Arch. f. Dermat. u. Syph. 173: 545-?1, 1936.

[136] Philpott, O. S., and Freshman, A. W.: Amyloid ... Cutis ... Arch. Dermat. & Syph. 33: 9?0-9?6, 1936.

CHAPTER XXXI

METABOLIC DISORDERS

Vitamin Deficiencies

Avitaminosis A —Vitamin A is a fat soluble heat resisting unsaturated alcohol which is easily destroyed by oxidation It is formed in the liver from its precursors the yellow or red carotenes which occur in widely differing amounts in fruits vegetables and animal fats The daily vitamin A requirement of the human organism is 3000 5000 I U

Deficiency of vitamin A causes night blindness because the visual purple and the visual violet develop from Vitamin A Xerosis conjunctivae is another early ocular symptom occurring together with the cutaneous epithelial changes A specific protective function of vitamin A against infections which was assumed earlier[2137 2139 140] is now doubted [1776 141]

The most often used test for vitamin A deficiency is the measuring of the dark adaptation of the eyes This is done by determining the threshold amount of light which must be used to illuminate a given surface in order to render it visible The readings after light and dark adaptation are then compared [214 2143] The value of the dark adaptation test for vitamin A deficiency has recently been questioned [144] The determination of the concentration of vitamin A in the blood plasma will probably be a better indicator of deficiency than the dark adaptation [1779] but so far only little work with spectrophotometric determinations of the vitamin A content in connection with skin changes has been done [2145]

The fat droplets containing vitamin A are highly fluorescent in ultraviolet light but lose this property rapidly in ultraviolet light [146] Surprisingly enough

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[2137] Schaaf F Ueber die Bedeutung der Vitamine in der Dermatologie Zbl 46 6 7-691 1933 1934

[2138] Fl rt M H Vitamins in Dermatology M Clin North America 26 47-64 1942

[2139] Pfannenstiel W and Scharlau B Der Einfluss gesteigerte Vitaminzufuhr auf experimentelle Staphylokokkeninfektion der Haut Ztschr f d ges exp Med 71 465-476 1930 Zbl 35 6 2

Pfannenstiel W Weitere Versuche über den Einfluss von Vitaminen und Calcium auf experimentell Staphylokokk infektionen d Haut Ztschr f d ges exp Med 77 18 2 5 1931 Zbl 39 290

[2140] Sternberg Th and Pillsbury D M Influence of Avitaminosis A on Experimentally Produced Cutaneous Infections in Rat Arch Dermat & Syph 35 247 2 0 193

[2141] Brunsting L A and Sheard C Dark Adaptation in Pityriasis Rubra Pilaris Arch Dermat & Syph 43 4 -61 1941

[2142] Carleton A and Steven D Keratosis Follicularis Arch Dermat & Syph 48 143 1 0 1943

[2143] Walters J D Dark Adaptation in Skin Conditions Ohio State M J 40 5 4 526 1944

[2144] Ruch D M Brunsting L A and Osterberg A E of Vitamin A Tolerance Test in Certain Cases of Dermatologic Disorders Proc Staff Meet Mayo Clinic 21 209- 17 1946

[2146] von Qu rn r F D mikroskopisch Nachweis von Vitamin im animal n Gewebe Klin Wchnschr 14 1213 1 17 1935

in examinations with the fluorescence microscope vitamin A has been found to be absent from the epidermis even after the feeding of high doses[2147]

It is likely that vitamin A is concerned with the lipids Experimental hyper vitaminosis A results in accumulation of cholesterol in the adrenals the skin and other organs[2148] so that lesions develop which are comparable to those of Schuller Christian s disease Circumscribed alopecia is also a feature of this experimental disease



Fig 86 Infant 16 mo th of age F lli ular hyperk ratosi in vitamin A d fici ncy with xerophthal mia (From Frazi r C N Hu C K and Chu F T Arch D rmat & Syph 1943)

Dermadromes —Hyperkeratinization as an effect of vitamin A deficiency on the epithelium has been known for a long time (Mori after Schaaf[2137]) In the rat it leads to the appearance of keratinized cells in the vaginal mucosa a phenomenon resembling estrus

In the human skin the effects of vitamin A deficiency are also dominated by hyperkeratinization [2149] Dryness caused by impaired function of the keratinized oil and sweat glands is the first symptom Frazier and Hu[2150] and inde

[2147]Cornbleet Th an I Popper H Properties of Human Skin Rev aled by Fluorescence Microscopy The Normal Skin The Vit min A Content of th Skin Arch Dermat & Syph 46 59-65 1942

[2148]Collazo J A and Rodriguez J S Hypervitaminos A durch Fütteru g von rei em A Vitamin an junge Ratte Klin Wchn chr 12 173 1734 1933

[2149] Mashkilleison L N B nyamovi h F B Krich vskaya E D and Shatamo a L V Vita mins in Pathog n sis and Treatm nt of Skin Di ases Am Rev Soviet Med 3 19 27 1945

[2150]Frazier C N and Hu C K Cutaneous Lesions A ociated With Defici ncy in Vitamin A in Man Arch Int Med 48 507 514 1931

pendently Loewenthal[2151] described a characteristic dermatosis which occurred frequently in persons who had lived on a diet deficient in vitamin A and who suffered from night blindness keratomalacia and/or xerophthalmia The eruption which was called *phrynoderma* or toad skin by Nicholls[215] healed after treatment with vitamin A or an adequate diet



Fig 287 —Male aged 14 years Diffuse follicular hyperkeratoses (phrynoderma) in vitamin A deficiency (From Frazier C N Hu C K and Chu F T Arch D rmat & Syph 1943)

Phrynoderma consists of disseminated somewhat grouped *perifollicular papules* with a central keratotic plug or spine In severe cases[2153] the papules are large flat or hemispherical sometimes acneiform without suppuration sometimes more like lichen planus Slate colored hyperpigmentation may occur in and around the lesions The eruption is usually abundant and symmetrical predominantly appearing first on the anterolateral aspect of the thighs and the

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[2151] Loewenthal L J A A New Cutaneous Manifestation in the Syndrome of Vitamin A Deficiency Arch Dermat & Syph 28 700-708 1933

[215] Nicholls L Phrynoderma A Condition Due to Vitamin Deficiency Indian M Gaz 68 681-686 1933

[2153] Fasal P Clinical Manifestations of Vitamin D ficiency in the Malay States Arch Dermat & Syph 50 160-166 1944

posterolateral aspect of the upper part of the forearms spreading from here to the extensor surfaces of the arms and legs the shoulders abdomen chest back and buttocks [2150] Itching is a frequent complaint There is absence of visible sweating so that the articular folds become dry and scaly Diffuse branny scaling ashing is also often noticeable especially in Negroes [2154] The colored skin is apt to lose its natural sheen [2151] The lack of oiliness helps to differentiate this papular eruption from acne

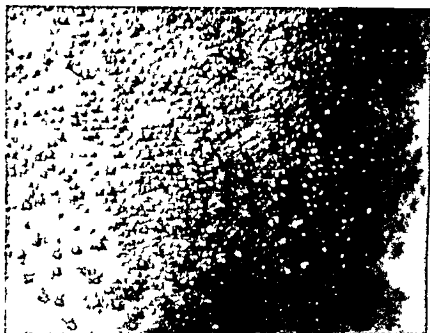


Fig 2 Mal aged 14 y ars I rojecting spin lik f llicular hyperkeratoses in vitami A d fi i ncy (From F azi r C N Hu C K a I Chu F T Arch Dermat & Syph 1943)

Comedones are common not only in adolescents but also in older persons Brittleness and grooving of the nail [2155, 2156] is a feature of avitaminosis A Loss of luster of the hair caused by dryness and alopecia are frequently observed phenomena [2154, 2157]

Phrynoderma usually precedes the *ophthalmic symptoms* [2158] which sometimes are completely absent Pillat[2159] describes a characteristic pigmentation of the

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[2154] Lehman E an l Rapaport H O Cutaneou Manifestations of Vitamin A D fici cy in Chil l n J A M A 114 386-393 1940

[2155] Reis F Contribution to Cutaneous Manifestations of Vitami A Defici ncy Chines M J 50 945-948 1936 Zbl 55 285

[2156] Gill S Alopecia Circumscripta Due to Vitamin A D fi i n y Cas Arch Dermat & Syph 51 110 111 1945

[2157] Pillat A E nähru gslehre Edited by W Stepp B lin 1939 Julius Spri g r

[2158] Frazier C N and Hu C K Nature and Di tribution According to Age of Cutaneous Manifestation of Vitamin A Deficiency (207 Ca es) Arch Dermat & Syph 33 8 5-852 1936

[2159] Pillat A Ueb r l e eigenartige Pigm ntl u g d r Bin lehaut bei den verschied n Fo m n der Vitamin A—Mang lerkranku g der E wachsen n Graef s Arch 127 575 597 1931

conjunctivae most marked in the caruncula plica semilunaris and the lower fornix The pigmentation may outlast the deficiency state after treatment with vitamin A



Fig 289 —Follicular hyperkeratosis in vitamin A deficiency with xerophthalmia (From Frazier C N Hu C K and Chu F T Arch Dermat & Syph 1943)

The *histopathologic* features are epithelial hyperplasia and hyperkeratinization with associated follicular keratinization and degeneration of the hairs as well as of the sweat and oil glands [159, 160] There is some inflammation in the corium but no pustulation The disease is not rare among children [154] as had been originally assumed The closer the age groups are to puberty the more likely they are to be affected [2161] This is in line with the well known tendency to follicular keratosis in acne juvenilis

Among children with xerosis of the skin without phrynoderma the sexes are equally affected In adult groups the patients are almost exclusively males [155] Straumfjord [162] has tried to explain the formation of vernix caseosa by the absence of the antikeratinizing vitamin A in later fetal life A small group of pregnant

[160] Moult F H Histopathology of Rat Skin in Avitaminosis A Arch Dermat & Syph 47 768-7 1943

[161] Frazier C N Hu and Chu Variations in Cutaneous Manifestations of Vitamin A Deficiency From Infancy to Puberty Arch Dermat & Syph 48 1 14 1943

[162] Straumfjord J V Vernix Caseosa A Manifestation of Vitamin A Deficiency West J Surg 48 341-3 1 1940

women who were treated with high daily doses of vitamin A during the last six months of pregnancy had babies with less vernix than usual

The response of phrynoderma and the other dermadromes to dietary *treatment* and vitamin A in daily doses of 100 000 to 300 000 I U is usually prompt within two to four months The sebaceous secretion was often restored within two weeks The recognition of a follicular kerato is as a specific manifestation of vitamin A deficiency by Frazier and Wu stimulated investigation of the nature of other follicular keratoses Peck[2163] found in eight out of ten cases of *Darier s disease* the blood vitamin A below normal and in nine cases he was able to improve the hyperkeratotic symptoms of this hereditary disease which up to then had been largely considered incurable The vitamin A level in the blood rose under treatment with approximately 200 000 units daily

Peck[2163 2164] believes Darier s disease to be a congenital disorder of the absorption of the vitamin A or of the conversion of carotene by the liver into the final product Peck s work has been confirmed in several instances[2163 2165] of this rare dermatosis but resistant cases have also been found[2163]

The follicular kerato is in *pityriasis rubra pilaris* (Devergie s disease) prompted Brunsting[2163] and Sheard to analogous investigations In three cases the threshold levels of dark adaptation were much higher than normal Under vitamin A treatment the night blindness and later also the cutaneous changes improved materially The vitamin A content of the blood has several times been found low[2165 166] The good results of treatment with vitamin A have been confirmed in some cases[2163 166]

Treatment with vitamin A has been found beneficial in various forms of excessive or abnormal keratinization particularly in dermatoses which have the features of dryness (asteatosis) and follicular or other hyperkeratosis such as acne vulgaris calluses corns[216 167 148] pruritus kraurosis vulvae[1903] lichen pilaris[2164] keratotic lichenoid plaques of the legs ichthyosiform erythroderma in Hodgkin s Disease with hepatic involvement[2169] scaliness of the external auditory canal[2170] nummular eczema[2171] brittleness of the nail[18] dryness of the skin in diabetes[2172] and keratosis blennorrhagica[30] It has been recommended in ointments for the treatment of burns and slow healing wounds and ulcers[2173] The

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[2163]Peck S M Ch rgin L a d Sobotka H Keratosi Follicularis (Dari r s Disease) a Vitamin A Defici ncy Dis a Arch D rmat & Syph 43 3 ? 3 1941

[2164]Peck S K ratosis Follicularis (Darier Diseas) Tr ated With Vitamin A Arch D mat & Syph 45 633 636 1942

[2165]Cornbl t T I pp H a d St igm r F Blood Vitami A a d Cutaneous Diseases Arch Dermat & Syph 49 103 106 1944

[2166]Wein r A L and Le in A A Pityriasi Rubra Pilari of Familial Typ Arch De mat & Syph 48 288 290 1943

[2167]Straumfjord J V Vitamin A Effect o A e Northwest Med 42 19 2 5 1943

[2168]Obermaye M F a d Frost K Som Phases of Vitami Th rapy in D rmatology Arch Dermat & Syph 51 309 31? 1945

[21] Glazebrook A J and Toma z wski W I hthyo if rm Atrophy of th Skin i Hodgkin Disease Vitamin A M tabolism Arch Dermat & Syph 50 85 89 1944

[2170]Jon s J H Vitami Therapy Laryng cop 52 80 194

[2171]Gross P Nummular Ec ma Arch D rmat & Syph 44 1060 1077 1941

[2172]Brazer J G an l Cu tis A C Vitami A Defici cy in Dia1 tes Arch Int Med 65 90 105 1940

[2173]Löh W Di Behandlung gro er flä h nhaft r Verbrennung n mit L bertran Chirurg 6 263 276 1934

cod liver oil containing salves are an example Vitamin A in high doses has been found ineffective in ichthyosis [2174]

All the mentioned *indications cannot yet be considered established* [2144] The therapeutic doses of vitamin A range from 50 000 to 200 000 units daily In spite of the fact that the blood serum level of vitamin A has been frequently



Fig 290 —Pityriasis rubra pilaris (Courtesy Dr M Jessner)

found to be low in widespread dermatitis eczema and psoriasis no curative effect of vitamin A therapy could be observed in such cases [2175] The level of vitamin A in the blood plasma of 55 patients with diverse dermatoses was essentially normal [2176]

[2174] Park I M Clark A W and Chargin L Vitamin A Studies in Cases of Ichthyosis Arch. Dermat & Syph 48 17-32 1943

[2175] Marchionini A and Patt L G Vitamin A— und Carotingehalt des menschlichen Blutserums bei Hautkrankheiten Arch f Dermat u Syph 175 419-437 1937

[2176] Cornbleet Th Popper H and Steigmann F Blood Vitamin A and Cutaneous Diseases Arch Dermat & Syph 49 103 106 1944

Carotenemia Xanthosis —Carotinemia *aurantiasis* (Baeltz after Kaufmann[2178]) or *xanthosis* (Von Noorden and Salomon) after Salomon[2177] (manifests itself by a yellow discoloration of the serum and of large areas of the skin The yellow color which may have canary ochre or sulfur shades suggests at first glance icterus but the sclerae are white and the mucous membranes are usually of normal color with the exception of the palate Another distinguishing feature is the distribution of the yellow pigmentation The nasolabial folds the axillae and the palms and soles are the sites of the most intensive discoloration in slight cases the only sites In contrast to icterus pruritus is absent unless caused by diabetes There are no complaints other than the disfigurement

The urine is light compared with an icteric urine although carotene is excreted in the urine

The history and physical examination almost regularly reveal that the patient had lived for a long time on a vegetarian diet that he is a diabetic or both

The yellow substance which causes the discoloration has long been identified as carotene The carotenes are red orange or yellow oxygen free hydrocarbon with 40 C atoms which by hydrolysis form the alcohol vitamin A All green leaves (not the yellow leaves in fall) carrots pumpkins yellow squash oranges especially some Japanese varieties and many other fruits contain carotenes Animals are unable to form carotene but they take it in and store it in the liver the fat the retina the corpus luteum and the adrenals It causes the yellow color of the butterfat the body fat and of the egg yolk Carotene does not appear in the sweat[2179] The horny layer of the epidermis has a marked affinity for carotene which explains the normal yellow hue of the palms soles and calluses[2179]

Carotinemia has often been seen in babies fed with carrots It was frequently observed during the First World War in Germany[2177] where at times most of the population was compelled to live almost exclusively on rutabagas carrots and other vegetables It is also prevalent in the Japanese inland where the fish and meat supply is scanty After feeding infants with carrots for a very long time the carotinemia may disappear in spite of continuing with the diet The system apparently adjusts itself and becomes able to step up the splitting of carotene The alimentary carotinemia particularly in infants is harmless and disappears quickly after a change in the diet (Diabetic carotinemia see chapter on Diabetes)

Vitamin D (viosterol and activated 7 dehydrocholesterol) is stored mainly in the liver but also in the skin and in other organs One of the known functions of vitamine D is the maintenance of the absorption of calcium and phosphorus from the intestinal tract[2180] The most important vitamin D deficiency disease is rickets

No dermatosis caused by vitamin D deficiency has been established Therapeutic success with daily doses of 50 000 to 400 000 units have been reported in

[2177] Salomon H Pseudoikterus nach Mohrrübengenuss München med Wchnschr 66 504 1919

[2178] Kauffmann and Drigalski Carotin Vitamin A im menschlichen Organismus Klin Wchnschr 12 306 309 1933

[2179] Edward E A and Duntley S Q Pigment and Color of Living Human Skin Am J Anat 65 1-33 1939

pemphigus [180, 181] but confirmation has remained lacking [218] The treatment has also been given a trial in psoriasis [18, 2183] and acne vulgaris Though 80 per cent satisfactory results were claimed in a large series [184] the method has not found general recognition [185]

Vitamin E comprises a group of more than 130 substances [17, 6] Experimental avitaminosis E manifests itself by sterility muscular dystrophy paralysis and other symptoms according to the animal used Many seed germ oils particularly that of wheat contain vitamin E which has so far not become of recognized dermatological importance Its successful use in acrodynia has been reported [186]

Vitamin K (menadione) occurs most abundantly in green leaves e g spinach alfalfa and cabbage It is also synthesized by several bacteria e g Escherichia coli Its absence inhibits the *prothrombin* formation in the liver When the prothrombin drop to about 10 per cent of normal in chicks kept on a vitamin K free diet the bleeding tendency appears [2187] In man obstructive jaundice through the absence of bile salts in the intestines impairs the absorption of adequate amounts of vitamin K and thus creates hypothrombinemia with a subsequent hemorrhagic tendency (Brown and Bancroft 1935 after Quick[890]) Therefore the picture of avitaminosis K is that of hemorrhagic disease which may cause purpuric skin manifestations In the adult it results most often from severe disease of the liver from short circuiting operations or chronic diseases of the intestinal tract For the role of vitamin K in the hemorrhagic disease of the newborn see chapter on newborn page 394

The Vitamin B Complex —According to Elvehjem[2188] the B complex consists of at least a dozen separate factors which vary widely in their chemical structure and physiological effects Deficiency in any one of the B vitamins is usually complicated by a deficiency in another B vitamin or by a deficiency in some other vitamin [189, 190]

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[180] Butt[w]orth T P mph[i]gu[s] Imp[r]ovement Following Vitamin D Arch De[r]mat & Syph 41 630 1940

[181] [illegible] H a[n]d Hamilton C M P[e]mphigus Controll[e]d by Vitamin D A[r]ch Dermat & Syph 39 1[0]517 1939

[182] Wright C S Vitamin D Th[e]rapy in D[e]rmatology Arch Dermat & Syph 42 145-154 1940

[2183] [illegible] Psoriasis Arthropathi[c]a Tr[e]at[e]d With Vitamin D Arch D[er]mat & Syph 41 931 1940

[184] Mayn[ar]d Vitami[n] Th[e]rapy in D[er]matology E[s]pecially Vitamin D f[o]r Acne Arch Dermat & Syph 41 842 857 1940

[185] [S]imps[on] C Ell[is] F A and K[ir]by Smith H Vitamin D i[n] th[e] Treatm[e]nt of Acne Arch D[er]m[a]t & Syph 41 835-837 1940

[186] Forsyth G [illegible] Di[se]as[e] Treated With Wh[e]at Germ M J Au[s]tralia 1 78 194[illegible] Ab[s]tr Arch D[e]rmat & Syph 45 [illegible]3

[2187] Qui[c]k A J Th[e] Co[a]gul[a]tion Def[e]ct in Sw[e]et Clover Di[se]as[e] and [i]n th[e] H[e]morrhagic Chick Di[se]a[se] [o]f Di[e]ta[r]y O[r]igi[n] A Co[nsi]d[e]ration of th[e] S[o]u[rc]e of [P]roth[r]omb[i]n Am J Phy[si]ol 118 260 71 19[3]7

[2188] El[ve]hj[e]m C A W[a]t[er] Soluble Vitamins H[a]ndbook of Nut[r]it[io]n Chi[c]ago 1943 Am[e]rican Medi[c]al Associati[o]n

[189] Jolliff[e] N Recent Ad[van]ces in Clini[c]al Appli[c]ations of the B Vitami[n]s J Am Di[e]tet A 17 [illegible]-11 1941

[190] [S]pi[e]s T D B[e]an W B a[n]d Ash[e] W F A Note o[n] th[e] [Use] of Vitamin B in Human Nutrition J A M A 112 2414 415 1939

A vitamin B deficiency should be suspected in indigent groups, in persons with peculiar food habits, e.g., alcohol addicts, in persons who live mainly on sweets and in dietary faddists, and in patients with diseases altering the vitamin B requirement. Jolliffe[2188] mentions in this connection prolonged abnormal strain, *manic depressive psychoses, fever of long duration, hyperthyroidism, pregnancy*, lactation, rapid growth, diarrhea of long duration, polyuria, gastrointestinal fistulae, and liver and stomach diseases.

Thiamine.—The richest sources of thiamine are yeast, pork, oatmeal, peanuts and other seeds, and liver. Spinach, tomatoes, oranges, apples and white unfortified bread are poor in this vitamin. Without the use of whole grain cereals or enriched bread, it is difficult to meet the adult daily requirement of *1.5 to 2.3 mg.*[2189] *Symptoms of thiamine deficiency*[2190] *include anorexia, fatigue*, insomnia, nausea, constipation, headache, precordial distress and a group of more tangible neurological manifestations like symmetric polyneuritis, especially of the legs, followed by central symptoms known as Wernicke's syndrome. Finally, there occurs a group of circulatory disturbances including edema, serous effusions and circulatory collapse. These circulatory manifestations occur in about one third of the patients with polyneuropathy. All the mentioned symptoms together with their many variations form the *beriberi* complex.



Fig. 291. Cheilitis and perlèche in riboflavin deficiency. (Courtesy Dr. O. H. [illegible] J. and The Upjohn Company.)

The only well established early, and therefore important, *skin manifestation in beriberi* is the burning of the soles of the feet and numbness of the dorsum and lower part of the ankle.[2191,2192] Glossitis, perlèche[2193] and other skin manifestations probably belong to associated avitaminoses. The expected pain relieving

[2191]Sharples, L. R.: *Burning Feet in Labourers on Sugar Plantations in British Guyana*, J. Trop. Med. 32: 358-360, 1929.
[2192]Strauss, M. B.: Article in the Vitamins, Chicago, 1939, American Medical Association.
[2193]Kagawa, S.: Ueber Rhagadenbildung am Mundwinkel bei der B-Avitaminose, Mitt. d. med. Gesellsch. zu Tokio 46: 1158-1164, 193[illegible]; Zbl. 43: 6[illegible]6.



Fig 29 —Loss of papillae filif rm s and increased r dn of th tongue in vitamin B defici ncy (Courtesy Therap ut c Notes Parke Davis & Company)

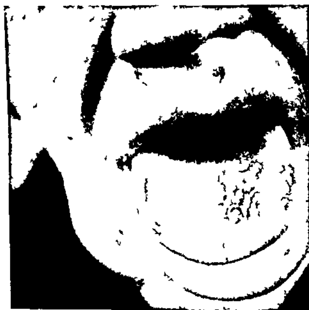


Fig ?93 Vitami B deficien y Loss of papilla filif rmes resulting in slick fissured tongue (Courtesy Wisconsin General Ho pital)

and curative effect of thiamin in herpes zoster and postherpetic neuralgia has failed to materialize.[194]

Riboflavin.—This vitamin is a yellow, crystalline, heat stable but light labile[194] substance. It functions as an enzyme in tissue respiration. Liver, milk and vegetables are the best sources. The daily minimal requirement can be met with one serving of liver or one quart of milk. Experimental ariboflavinosis causes retarded growth, dermatitis and cataract in rats, paralysis from myelin degeneration in chicks and dogs, and opacities in the cornea of various animals.

Dermadromes.—In man, vascularizing keratitis is usually the first to appear. It may be followed by glossitis and dermadromes. Sebrell and Butler[195] gave eighteen adult women the so-called Goldberger-Tanner diet,[196] which does not contain meat, milk or yeast, but consists mainly of lard, cornmeal, casein,



Fig. 91. Vitamin B deficiency ... Tongue ... inflamed ... papillae ... started ... appear. (Courtesy Dr. Garrett Cooper.)

tomato juice, cod liver oil and other items low in riboflavin and nicotinic acid. Within three to four months ten out of the eighteen persons developed pallor of the lips at the angles of the mouth without involvement of the buccal mucosa. This pallor was soon followed by maceration, bilateral, superficial transverse *fissures extending downward from the angle, in some instances as much as one half of an inch.* Thus typical perleche developed. There was little inflammatory reaction. The lesion remained moist and became covered with a yellow crust. The lips became eroded and red along the line of closure. Sebrell and Butler[195] called this labial affection *cheilosis*. In addition to the cheilosis there was a fine, seborrheic desquamation on a slight erythema in the nasolabial fold, on the alae nasi, in the vestibule of the nose and on the ears.

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[194] Rattner, H., and Roll, H. C.: Herpes Zoster ... Vitamin B. J. A. M. A. **112**: 2585, 5-6, 1939.

[195] Sebrell, W. H., and Butler, R. E.: Riboflavin Deficiency in Man. Publ. Health Rep. **53**: 2282-2284, 1938.

[196] Goldberger, J., and Tanner, W. F.: Pellagra—... the Action of Dried Beans, Casein, Dried Milk and Brewer's Yeast. Pub. Health Rep. **40**: 54-80, 192_.

Other authors[2189, 2197] observed *filiform excrescences of a seborrheic nature* in the nasolabial folds and their surroundings resembling urea frost in conditions which they felt to be due to riboflavin deficiency *

The experimental cheilosis healed promptly on crystalline synthetic riboflavin while nicotinic acid failed to cure it Spontaneous cases of cheilosis are not infrequently found among alcoholics and other persons liable to become vitamin B deficient Jolliffe[2197] et al demonstrated that many of these spontaneous cases of cheilosis responded to synthetic riboflavin but not to thiamin nicotinic acid or pyridoxin (also see Finnerud [2198])

In some cases of ariboflavinosis the tongue has been found purplish red fissured and with enlarged papillae [2199] Riboflavin in doses of 2 5 to 50 mg given by mouth heals cheilosis from riboflavin deficiency sometimes strikingly in a few days [2196] but of course fails to do so when the perlèche or cheilitis are due to other causes [2198] e g ill fitting dentures or sensitivity to light Cheilosis is also a common feature of pellagra in children [2200]

Sydenstricker [2201] and others have described *ocular* symptoms especially an early vascularizing keratitis accompanied by inflammation of the limbic plexus and conjunctiva bulbi in the interpalpebral space Photophobia is a characteristic complaint The slit lamp is necessary for early diagnosis The keratitis resembles the form often associated with rosacea but it is bilateral responds to riboflavin and shows a different vascular pattern

The validity of the syndrome cheilosis keratitis and glossitis as a manifestation of ariboflavinosis has recently been doubted because of the failure of riboflavin to cure it in 20 cases [2202] Riboflavin has lately been recommended in the treatment of eczema [2203, 2204]

Rats with chronic hyporiboflavinosis showed in contrast to other avitaminoses a heavy infestation with lice which disappeared after feeding them riboflavin [2205]

Nicotinic Acid (Niacin) Pellagra —Nicotinic acid (niacin) and nicotinic acid amide (niacin amide) are the components of two pairs of heat stable (Chick and Roscoe[2206]) coenzymes concerned with respiration and carbohydrate metabolism [188] A deficiency disease in dogs called blacktongue has since the work of Goldberger and his coworkers in the early twenties been con

* These pseudo-seborrheic changes should not be confused with seborrheic dermatitis which is accompanied by oily hair and skin

[2197]Jolliffe N Fein H D and Rosenblum L A Riboflavin Deficiency in Man New England J Med 221 921 6 1939

[2198]Finnerud C W Perlèche Its Nosologic Status J A M A 126 737 740 1944

[2199]Jolliffe N The Preventive and Therapeutic Use of Vitamins J A M A 129 613-617 1945

[2200]Hou H C Riboflavin Deficiency Among Chinese Cheilosis and Seborrheic Dermatitis Chinese M J 59 314 1941 Abstr Arch Dermat & Syph 46 561

[2201]Sydenstricker V P Sebrell W H Cleckley H M and Kruse H D Ocular Manifestations of Ariboflavinosis J A M A 114 2437 44 1940

[2202]Machella Th E and McDonald P R B Vitamin in the Human Subject VI Failure of Riboflavin Therapy in Patients With the Accepted Picture of Riboflavin Deficiency Am J M Sc 205 214 ? 3 1943

[2203]Landor J V Deficiency of Vitamin B_2 Lancet 1 1369 1370 1939

[2204]Kristensen K P and Vedel S V Treatment of Eczema With Vitamin B Complex Lancet 1 170 1940

[2205]György P Pediculosis in Rats Kept on a Riboflavin-deficient Diet Proc Soc Exper Biol & Med 38 383 1938

[2206]Chick H and Roscoe M H Heat-Stability of Vitamin B_2 Biochem J 24 105 11 1930

sidered analogous to human pellagra. In 1937 Elvehjem discovered that nicotinic acid would cure canine blacktongue. Deficiency of nicotinic acid is generally believed to be the main cause of pellagra, though clinical pellagra is considered now to be a multiple vitamin deficiency,[2207, 2208] which is often associated with symptoms of beriberi,[2209] ariboflavinosis[2210] (Hou, after Ottenstein[2]), sprue,[2211] and scurvy.

Liver and yeast are the richest natural sources of nicotinic acid. Corn contains only about one fifth of the niacin content of wheat, and the refined flours of both grains lose almost the entire amount. Nevertheless, even refined wheat flour still contains three times as much niacin as refined corn flour. The peculiar scarcity of niacin in corn accounts for the frequency of pellagra in countries where the diet of the poor consists predominantly of corn flour products. The first medical writer on pellagra, the Spaniard Casal, in 1762 already suspected the use of corn flour in the poor peasant population as one of the causes of pellagra.[2212] We know now that other deficient diets may cause pellagra too. Alcoholism and chronic gastro-intestinal disease are the most important *causes of pellagra in countries without endemic pellagra*.[2213] Among 102 cases in Baltimore, about one third were due to alcoholism, one third due to malnutrition, and one third secondary to other diseases.[2214, 2216] Chronic gastric ulcer, cancer of the stomach, and surgical removal of large parts of the stomach or bowel are conditions which predispose to pellagra.[2217]

The main *centers of endemic pellagra* are found in some warm mediterranean countries and in the southern U.S.A. The tropics, as well as the cooler climates, have only sporadic cases, mostly alcoholics, insane, or patients with gastric disorders. The incidence has become smaller in the main centers, e.g., Italy[2218] (Lavinder, after Seale Harris[2211]), where the morbidity of 104,067 in 1881 had diminished to 55,029 in 1905, probably due to improved living and eating conditions. At the same time the mortality was reduced to about one tenth. Thus in the last decades pellagra has become a rare disease in the classical pellagra country. A decided trend to the better also prevails in the southeastern U.S.A., where the incidence has been reduced by more than 50 per cent from 1929 to 1936.[2215] Today pellagra is no longer a major public health problem

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[2207] Gordon, F. S., and Sevringhaus, E. L.: Vitamin Therapy in General Practice. Chicago, 1940, The Year Book Publishers, Inc.

[2208] Elvehjem, C. A.: Relation of Nicotinic Acid to Pellagra. Physiol. Rev. 20: 249, 1940.

[2209] Snijders, E. P.: Pellagra. Nederl. tijdschr. v. geneesk., pp. 949-950, 1933. Zbl. 46: 187.

[2210] Sydenstricker, V. P., Geeslin, L. E., Templeton, C. M., and Weaver, J. W.: Riboflavin Deficiency in Human Subjects. J.A.M.A. 113: 1697-1700, 1939.

[2211] Harris, S.: Clinical Pellagra. St. Louis, 1941, The C. V. Mosby Co.

[2212] Merck, L.: Pellagra. Zbl. 17: 241-265 and 369-411, 19..

[2213] Klauder, J. V., and Winkelman, N. W.: Pellagra Among Chronic Alcoholic Addicts. J.A.M.A. 90: 364-371, 1928.

[2214] Boggs, T. R., and Padget, P.: Pellagra, 102 Cases. Bull. Johns Hopkins Hosp. 50: 21-32, 193.

[2215] Wheeler, G. A., and Sebrell, W. H.: Control of Pellagra. J.A.M.A. 99: 95-98, 1932.

[2216] Spies, T. D., and de Wolf, H. F.: Observation on the Etiological Relationship of Severe Alcoholism to Pellagra. Am. J. M. Sc. 186: 521-525, 1933.

[2217] Eusterman, G. B., and O'Leary, P. A.: Pellagra Secondary to Benign and Carcinomatous Lesions and Dysfunction of the Gastrointestinal Tract. Thirteen Cases. Arch. Int. Med. 47: 633-649, 1931.

[2218] Lutrario, A.: La pellagre qui disparaît en Italie. Bull. Offic. internat. d'hyg. pub. 28: 88-1.6, 1936.

in the Union though it is far from being stamped out In 1938 3 205 deaths from pellagra occurred mostly in the southeastern states It is remarkable that the southwest has a very low pellagra rate

The *ages* between 20 and 45 years seem to be most susceptible (Lavinder after J Jadassohn[2219]) but no age group is immune Many large statistics show a dominance of the female *sex* Menstruation pregnancy and lactation are provoking factors The distribution of the lesions suggests strongly that *sunlight* is an important pathogenetic element yet a great number of observations of typical lesions in covered skin (vulva) and of lesions restricted to the typical areas in children who did not wear any clothes prove that exposure to light is not the only provoking factor[2219] though one of great importance in the eruptive stage[2220] or after a prolonged deficient diet[22 1] Some authors even claim a beneficial influence of sunlight in pellagra in some stages[2222] (for extensive discussion of the sunlight factor see also Seale Harris[2211])

Lack of a *gastric* intrinsic anti pellagral factor [3] and failure of the liver to store and utilize nicotinic acid are much discussed pathogenetic factors[2211]

The *word pellagra* is derived from the Italian *pelle agra* sharp burning skin or from the Latin *pellis aegra* —sick unhealthy skin The skin manifestations however though characteristic do not represent the most serious part of the syndrome

Usually the disease[2 19] *starts* in the spring of the year, with increasing lassitude and muscular weakness especially of the legs which make the patients slow moving and resort to the use of canes a suggestive symptom well known to physicians in pellagra regions

Already in this early stage *burning* of the seemingly still normal skin particularly of the feet a burning sensation in the throat which cannot be soothed by cold water and other *paresthesias* cause discomfort The patients avoid the heat and lie uncovered in bed Headache and sudden attacks of dizziness or falling without coma convulsions or nystagmus are typical *nervous symptoms* The reflexes are increased the pupils are small [2224] Psychoses of widely varying seriousness develop frequently The facial expression of the patient is often a worried fearful melancholic or stuporous one[2 5] Such patients cry easily and are depressed sometimes in realization of the deterioration of their faculties In severe cases hallucinations depression even mania delirium suicidal at

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[2219] Merck L and Jadassohn J Die Pellagra Handb d H u Gk 4 2 377 587 1933

[22 0] Flinke R Die Lokalisation der pellagrösen Hautveränderungen Schweiz med Wchnschr 64 150-153 1934

[2221] Smith D T and Ruffin J M Effect of Sunlight on the Clinical Manifestations of Pellagra Arch Int Med 59 631-645 1937

[2222] Spies T D Pellagrous Dermatitis and Sunlight Arch. Int Med 56 920-926 1935

[2223] Sydenstricker V P Armstrong E S Derrick C J and Kemp P S On the Existence of an Intrinsic Deficiency in Pellagra Am J M Sc 192 1 9 1936

[24] Kleinmann H Beiträge zur Frage der Pellagra Virch d lo 23 1659 1694 1930 Zbl 38 783

[2225] Rill J H Die Hauterscheinung n d r Pellagra, Dermat Ztschr 58 30-312 19-0 also Zbl 34 133 136

tempts and other manifestations of psychoses develop [2226, 2227] On the other hand psychosis with a long confinement to institutions is a predisposing factor to pellagra [2228]

The internal symptoms are dominated by various phases of inflammation of the *gastrointestinal tract* These disturbances most often account for a fatal outcome [2210] The oral symptoms will be described later

Anorexia is an early symptom Nausea vomiting and diarrhea are common though greatly varying in intensity Free HCl is absent in more than 66 per cent [2230, 2231] and the pepsin content is low The stool no matter of what consistency are nearly always foul [2207] *Anemia* is present in about 50 per cent [2232, 2234] *Diabetes insipidus* has been observed frequently Urinary *porphyrin* has been found according to the extent and acuity of the skin manifestations It is a coproporphyrin which has but a weak light sensitizing effect Porphyrin excretion was



Fig 15 Pellagra Extensive dermatitis on right hand following accidental unilateral exposure to sunlight (From Harris S Jr Clinical Pellagra The C V Mosby Co)

[2226] Slotopolsky B Zum Vorkommen pellagroider Erkrankungen bei Alkoholikern und Geisteskranken Schweiz med Wchnschr **62** 297-301 1932

[2227] Chotzen F Klinische Beitrag zur Kenntnis der Pellagrapsychosen Ztschr f d ges Neurol u Psychiat **148** 170-210 1933

[2228] Georgi F and Beyer A Zur Klinik und Genese der Pellagra Monatschr f Psychiat u Neurol **76** 296-355 1930

[2229] Franke G Ueber Pellagra in Irrenanstalten Psychiat neurol Wchnschr **35** 461-465 1933

[2230] Szöcs M and Mares C Beitrag zum Studium der Magensaftes bei der Pellagra Der Einfluss des Histamin auf die Achlorhydria der Pellagra Rev Clint med **19** 237? 377 1930 Zbl **39** 537

[2231] Guthrie J B Achlorhydria in Pellagra J Trop Med **35** 71 74 103

[2232] Flinker R Das Blutbild bei Pellagra Folia haemat **49** 148 155 1933 Zbl **45** 459

[2233] Turner H Pellagra Arch Dermat & Syph **25** 960 96 1932

[2234] Rassulev J A Diabetes insipidus bei Pellagra Arch f Schiffs u Tropen Hyg **36** 481-489 1932

found negative in the interval between the attacks [2235] Urinary porphyrin has occasionally been found in alcoholics with or without pellagra [2236] *Fever* is generally absent but in some cases a spiking fever with diarrhea may create a typhoid resembling rapidly fatal disease [2237, 2238]

Dermadromes —Skin manifestations of pellagra appear in the majority of the cases [2219] They do not cause such dangerous complications as the gastro intestinal and neurological symptoms but they are of great diagnostic even path



Fig 296 —Early pellagrous dermatitis over the patellae (Courtesy Dr Henry Field Jr and the Upjohn Company)

ognomonic importance Together with the sometimes dubious internal complaints they give the syndrome of pellagra its character as a well defined entity

[2235] Beckh W Ellinger P and Spies T D Porphyrinuria in Pellagra Quart J Med 6 305 319 1937

[2236] Kark R and Meiklejohn A P Pellagra and Porphyrinuria Am J M Sc 201 380-385 1941

[2237] Ginsburg D Sporadic Cases of Pellagra in Northern Russia Sovet vest derm 9 575-58 1931 Zbl 41 64

[2238] Margarot J and Rimbaud I Typhose pellagreuse Bull Soc Franç de dermat et syph 38 1361 1364 1931

The outbreak of typical *pellagral erythema* occurs suddenly sometimes preceded by a premonitory deciduous macular eruption[7,19] on the dorsa of the hands The true erythema of pellagra appears most frequently at first on the *dorsa of the hands In contrast to eczema this lesion is solid and well defined* Even in sunlight exposed and tanned forearms the pellagral erythema rarely extends higher up than the wrist line The palms remain free The pellagral erythema frequently stops at the knuckles but it may invade the extensor surfaces of the fingers [19]



Fig 97 —Pellagra collar of Casal (Courtesy Dr M J [illegible])

Occasionally the erythema affects the flexor aspects in a strap or cuff like bridge if this occurs it is considered an important diagnostic sign [4,5] The instep is the site of an additional erythema Here the inflammation extends from a line right above the ankles to the base of the toes In analogy to the hands the dorsa of the toes are only occasionally involved The erythema may also appear on the face The bridge of the nose is most frequently erythematous but diffuse or confluent always symmetric patches may occupy the whole face In the confluent type polycyclic patterns may appear Facial erythema is more often encountered in women and children than in men and it is often inconspicuous [2,5] Narrow bands of skin along the hair line and around



Fig 298 — Pellagra Collar of Casal Cheilitis (From Harris Seale Clinical Pellagra)

the mouth remain normal This mask like distribution is similar to that of chloasma

The fourth typical site of pellagral erythema is a ring of varying width around the entire neck This is called the necklace or collar of Casal In the typical instances Casal s necklace extends into the sternal area as a berloque shaped appendix

The elbows knees (Bass after Seale Harris[2211]) shoulders scrotum perineum vulva and infra mammary areas[2239, 2240] are some of the less common sites Sym

[2239] Costello M J Pellagra in Unusual Locations Arch Dermat & Syph 46 7[illegible]4 1942

[2240] Riordan T J Cellis S and Rubinowitz A M Unusual Sites of Lesions in Pellagra Arch. Dermat & Syph. 46 661-664 1942

metry is a pronounced, sometimes astonishing feature.[2-5] The skin on which the erythema develops is often slightly edematous. At first the erythema consists of confluent pink blotches, but within a week it takes on a bright scarlet red color which later has a copper or mahogany hue.[2-5]

A few days after the appearance of the erythema the epidermis *cracks and fissures* develop. In some cases vesicles, blisters, pustules and other forms of secondary infection may appear, with a predilection for the hair follicles of the dorsa of the fingers. These follicles are often blackened with non removable

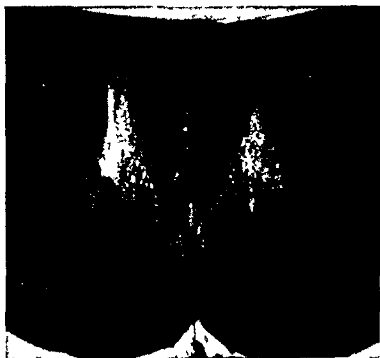


Fig. 91.—Vulvitis in pellagra. (From Harris, Seale: Clinical Pellagra.)

dirt. In the early part of the second week the erythema reaches its peak. A pink halo up to 2 cm in width may surround the lesions. A few days later the acute symptoms recede and ichthyosiform keratosis, peeling, deep fissuring and increasing pigmentation become the dominating features. The pattern of ridges and furrows is coarsened. *Follicular keratoses* appear in the erythematous areas. On the hands they may be inconspicuous, but on the bridge, the tip and the sides of the nose and in the *nasolabial folds* they may form grater-like patterns.

This follicular hyperkeratosis about the nose has been referred to as seborrhea.[2, 3] The facial follicular hyperkeratosis is a frequent and characteristic clinical feature of pellagra.[19]

The centers of the pellagral areas begin to clear up during the fourth week. The horny layer comes off in large flakes, sometimes in sheets of the size of the entire lesion. A scaly, hyperkeratotic margin may remain for some time.

The typical attack of pellagral erythema is over in 6 to 10 weeks. Pellagra usually occurs in *repeated attacks* mostly in spring and early summer although recurrences in fall occur occasionally. In winter time the patient is usually free of symptoms. The repeated attacks of erythema on the dorsa of the hands leave the skin in an increasingly *atrophic* condition which of course is not reversible.

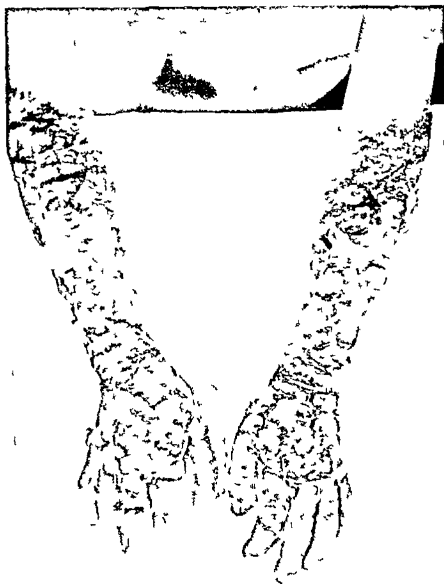


Fig 300 Neglected pellagra Thickened fissured and pigmented lesions extending far beyond the commonly involved dorsa of the hands (From Harris Seal Clinical Pellagra.)

Longitudinal yellowish stripes (sometimes referred to as striae) are caused by underlying extensor tendons which can be seen through the thin atrophic skin in moderately strong day light.[611,7795] *Oral manifestations* occur in about one half of the cases (Sandwith after J. Jadassohn[7719]). They are important because some of them, e.g., burning and salivation, are among the earliest symptoms. The descriptions of the *tongue* in pellagra vary. Swelling and coating are early

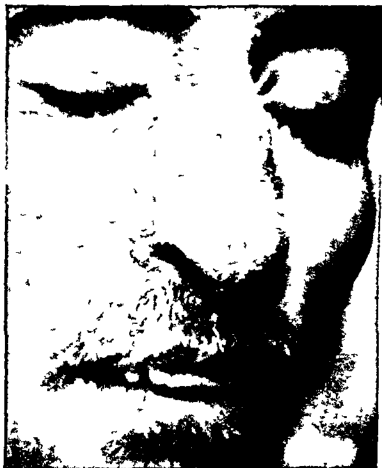


Fig. 301. So-called "seborrhea" of the nose in pellagra. (From Harris, Seale: Clinical Pellagra.)

symptoms. Denudation may occur on the margins and on the tip while the dorsum remains coated.[2219,7795]

In fully developed cases, the fungiform papillae may be reddened and swollen (raspberry tongue) or, in later stages, atrophic, thus giving the appearance of a slick, bald, thin tongue. Fissures and ulcerations, black hairy tongue, brown coating, ulceration and other lesions have been observed. In acute stages the entire oral mucosa may be fiery red. Aphthous lesions are common.[2218]

The *lips* may show small red erosions and there may be angular fissures Plaut Vincent s infection of the gums is a common finding in pellagral stomatitis [41]

Vaginitis and vulvitis with much discharge and occasionally edema of the clitoris and labia minora is often called an important or even pathognomonic symptom



Fig 30 —Pellagra Typical dermatitis of the feet and of the patella region (From Harris Seal Clinical Pellagra)

The *nails* are usually not affected The *hair* is often shed during the attacks and complete alopecia has been seen to develop The loss of the lateral part of the eyebrows is frequent and may have some endocrinological significance (see

[41] Kassirsky J and Burova L Zur Klinik der Pellagra in Mittelasien Arch f Schiffs u Tropen Hyg 36 323-336 1932

chapter on Endocrines) Of interest is the observation of koilonychia and achylic anemia (Plummer Vinson syndrome) in a woman with pellagra [1210]

Epithelioma of the skin is a surprisingly rare complication in pellagral dermatitis [1211]

The occurrence of repeated seasonal attacks has already been mentioned Many *variations in course* and symptomatology have become known so that the diagnosis in nonendemic cases may be extremely difficult or even impossible in the absence of skin manifestations The term *pellagra sine pellagra* is used for such cases Internal symptoms usually precede the erythema for a considerable time [1212] According to Merck the erythema rarely remains absent longer than one year after the first symptoms Slight erythemas may well pass unnoticed It is probably for this reason that the incidence of dermadromes has in some large series only been 45 per cent [1213] There is no relationship between the degree of the erythema and the severity of the internal symptoms



Fig 303 Pellagra Typical dermatitis of the dorsal aspect of the hands Fissures and crust From Harris S al Clinical Pellagra)

Of great interest are the *variations of the clinical picture* in various countries and in the same country at different times Thus Casal s necklace and the involvement of the instep areas is relatively common in southern Europe especially the Balkans and rare in the U S A

[1210] Mollow W Nagelveränderungen bei Pellagra Arch f Schiffs u Tropen Hyg 41 381-383 1937

[1211] Rutledge W U and Kelly R Epithelioma Secondary to Pellagrous Dermatitis Arch Dermat & Syph 23 107 1075 1931

[1212] Efremow V Etiology Pathogenesis and Prophylaxis of Pellagra M I para Itol I para it bolez 2 261 276 1933

The post mortem *pathology* is unrevealing The most striking feature is the severe hepatic atrophy or fatty degeneration As can be expected the skin shows keratosis parakeratosis pigmentation and atrophy according to the stage There is degeneration of the elastic fibers and perivascular infiltration and hyalin degeneration of the vascular walls[2 45] The unaffected skin also shows hyper keratosis atrophy and inflammation though in a lesser degree[246]

The *diagnosis* is a clinical one since satisfactory laboratory methods have not yet been worked out One has to consider eczema in which there are no mucosal symptoms and no atrophy and erythema exudativum multiforme in which the primary le ion is a coin shaped erythematous urtica often with a central vesicle Acrodermatitis atrophicans takes a slow nonseasonal course and has its typical localization and pityriasis rubra pilaris is nonseasonal and there is no pronounced involvement of the typical pellagra sites although niacin is reportedly effective [47] The diagnosis of pellagra is easy in endemic and fully



Fig 304 Atroph tongu in p llagra (F om Harri S al Cl i l l llagra)

developed ca es but difficult in spor idic and incomplete cases The typical sites the sharply outlined lesions the seasonal attacks atrophy nutritional peculiarities including chronic gastrointestinal disease and alcoholism and the combination of internal and skin manifestations will often assure the diagnosis if its possi bility once enters the physician s mind Incomplete syndromes[248] may cause great difficulties in the differentiation from pernicious anemia [49 2 50] sprue Addison s disea e and other entities

Arutli ow Mat riali n zur Ferschung d r Pellagra Diss B ku 1933 Zbl 45 457

[246] Moore R A Spies T D and Coope Z K Histopathogy of the Ski i P ll gra Arch D rmat & Syph 46 100-111 194

[47] Gross I ity lasis Rul Pil ris and Vitamin Th rapy A h D rmat & Syph 44 270-7 1940

[48] Wheel r G A A Not on th Hi to y of P llagra in th U ited Stat s Pub H alth R p 46 -3 79 1931

[49] Spies T D l y W l Chi n A B R latio hip of P ll gra t P l iou An mia Proc or F pe Bi l & Med 32 3 -330 1934

[250] Krjukoff A Blut u d Blutbildung bei schw ren Fäll n on Pell gra Folia ha mat 45 196-206 1931 Zbl 40 6

As a diagnostic sign one has to add successful *treatment* with nicotinic acid[2251] and a balanced diet. More than one thousand successfully treated cases (nicotinic acid) were reported in 1941 when Seale Harris published his monograph on pellagra. Oral treatment with nicotinic acid in divided doses totaling 500 mg daily supplemented by vitamin B complex and vitamins A, C, D and E is recommended (Spies et al. after Gordon and Sevringhaus[2259]). After a week 100 mg per day is sufficient. Ruffin and Smith[2251] advise injections of about 100 mg daily. Injections and larger doses by mouth are followed by flushing of the face together with a feeling of heat and tingling.[2258] This harmless side-effect can be avoided if the nicotinic acid is given with the meals or replaced by nicotinic acid amide.[2252]

A high caloric *diet* with the emphasis on meat, liver, eggs, milk and fresh vegetables, removal from slum housing and reduced exposure to sunlight are other important therapeutic factors. Stomach preparations (ventriculin) have been recommended by several authors.[2254-2256] This medication is based on the discovery of an intrinsic pellagra preventing factor in the gastric juice.[2255]

The *prognosis* is now better and recovery is often dramatic unless irreversible damage to the nervous and gastrointestinal systems or severe cachexia has developed. In spite of liver diet or medication the mortality in large American series was still 20 to 31[2257] and even 50 per cent[2258] 10 years ago but almost zero in private practice.[2259] With the use of nicotinic acid and other vitamins the mortality has probably been lowered. Many authors stress the importance of prolonged treatment after clinical cure.

The pellagra preventing effect of nicotinic acid has been proved.[2259]

Pyridoxine has been used with encouraging results in the treatment of adolescent *acne*. The doses varied from 50 to 250 mg daily in divided doses.[2260] Seborrhea and an acrodynia resembling syndrome have been seen in pyridoxine deficient rats.[2260-2262]

[2251] Ruffin, J. M., and Smith, D. T.: Treatment of Pellagra With Special Reference to the Use of Nicotinic Acid, South. M. J. 32: 40-4, 1939.

[2252] Goldsmith, G. A., and Cordill, Sh.: The Vasodilating Effects of Nicotinic Acid, Am. J. M. Sc. 205: 204-208, 1943.

[2253] Lucksch, F.: Pellagraprobl. m. Med. Klin. 33: 159-161, 1937.

[2254] Petri, S., and Warsche, O.: Treatment of Pellagra and Polyneuritis With Stomach Preparations, Hospitalstid. 79: 1003-1008, 1936; Zbl. 86: 309.

[2255] Petri, S., Wanscher, O., Stubbe Teglbjaerg, E., and Stubbe Teglbjaerg, H. P.: Treatment of Pellagra With Stomach Preparations and the Gastrogenic Etiology of Pellagra etc., Acta med. Scandinav. 93: 450-486, 1937; Zbl. 88: 350.

[2256] Stubbe Teglbjaerg, H. P.: Neurological Problems in Pellagra, Treatment With Ventriculin, Hospitalstid. 80: 841-848, 1937.

[2257] Smith, J. H.: Pellagra, Resume Internat. Clin. 2: 120-134, 1933.

[2258] Sydenstricker, V. P., and Armstrong, F. S.: 440 Cases of Pellagra, Arch. Int. Med. 59: 883-891, 1937.

[2259] Spies, T. D., Grant, J. M., Stone, R. F., and McLester, J. B.: *Recent Observations on 600 Pellagrins*, Nicotinic Acid in Prophylaxis, South. M. J. 31: 1231-1237, 1938.

[2260] Jolliffe, N., Rosenblum, L. A., and Sawhill, J.: The Effects of Pyridoxin (Vitamin B_6) on Persistent Adolescent Acne, J. Invest. Dermat. 5: 143-148, 1942.

[2261] Eckhardt, I. E., György, P., and Johnson, L. V.: Presence of Factor in Blood Which Enhances Bacterial Growth Activity in Relation to Riboflavin, Proc. Soc. Exper. Biol. & Med. 46: 405-409, 1941.

[2262] Sullivan, M., and Nicholls, J.: Nutritional Approach to Experimental Dermatology. Nutritional Dermatoses in the Rat. II. Vitamin B_6 Deficiency, J. Invest. Dermat. 3: 309-345, 1940.

According to Gordon and Sevringhaus[2262] pyridoxine is able to heal cheilosis quicker than riboflavin[2263] Some pellagra cases may heal only after addition of pyridoxine to the other vitamins[2190] The healing effect in seborrheic eczema atopic dermatitis and eczema[2264] still lacks confirmation

No cutaneous manifestations in man have definitely been related to deficiencies of *panthothenic acid choline* and *biotin* Panthothenic acid prevents the greying of the hair in rats fed on a B complex free diet[65] A substance in uncooked eggwhite called *avidin*[2266] is able to inactivate the vitamin *biotin* (vitamin H) Dermatitis of the feet in the chick and alopecia in rats fed on a diet containing much raw egg white have been observed and some data pointing to analogous phenomena in man are available[67 2268] The so called egg white injury in the rat has been cured by the addition of excess biotin[2189] to the eggwhite rich diet or by inactivating the avidin by cooking *A para amino benzoic acid* deficient diet causes graying of the fur of rats which can be cured by feeding this substance[2269] *There is some evidence that repigmentation of gray* hair in man may be stimulated by oral administration of para amino benzoic acid or calcium panthothenate The changes produced in some persons were only of theoretical value since in the majority of the cases with any change at all an unsightly yellow or greenish cast was produced sometimes together with scattered wiry black hairs[70 27] No satisfactory restoration of the hair color which could compete with dying has been accomplished[73] Some results of prolonged oral medication with para amino benzoic acid in vitiligo have been reported[2 71]

Inositol is required to maintain the fur of the mouse[2274] Stryker and Halbeisen[2275] observed that 32 out of 42 cases of unexplained and noncharacteristic *dermatitis about the neck* and face were accompanied by moderate macrocytic anemia These cases responded at once to proper diet and liver extract which in the opinion of the authors was due to the vitamin B complex

Avitaminosis C—Scurvy—*Vitamin C or ascorbic acid* occurs in many animal and plant tissues especially *in the adrenal cortex from which it was first*

[2263] Mach lla Th E Studies of the B Vitamin in the Human Subject Am J M Sc 203 114 1942

[2264] Wright C S Samitz M H and Brown H Pyridoxin in Dermatology Arch Dermat & Syph 47 6 1-653 1943

[2265] Unna K Richard G V and Sampson W L Studies on Nutrit Achromotrichia in Rats J Nutrition 22 553-563 1941

[2266] György P Rose C S Eakin R E Snell E E and Williams R J Egg White Injury Non Absorption of Biotin Science 93 477-4 8 1941

[2267] Sydenstricker V I Singal S A Briggs A F De Vaughan N M and Isbell H Egg White Injury in Man and Its Cure With Biotin J A M A 118 1199-1200 1942

[2268] Williams R H Clinical Biotin Deficiency New England J Med 228 47 25? 1943

[2269] Ansbacher S p-aminobenzoic Acid a Vitamin Science 93 164 165 1941

[2270] Brandaleone H Main E and Steele J M Effect of Calcium Pantothenate and Para aminobenzoic Acid on the Gray Hair of Humans Proc Soc Exper Biol & Med 53 47-49 1943

[2271] Sieve B Clinical Effects of a New B-Complex Factor Para-aminobenzoic Acid on Pigmentation and Fertility South Med & Surg 104 135-139 1942

[2272] Can Hair Turn White Over Night? J A M A 121 161 16 1943

[2273] Eller J J and Diaz L A Vitamins for Gray Hair New York State J Med 43 1331 1943

[2274] Woolley D W Nature of Anti Alopecia Factor Science 92 384-385 1940

[2275] Stryker G V and Halbeisen W A Determination of Macrocytic Anemia as Aid in Diagnosis of Certain Deficiency Dermatoses Arch Dermat & Syph 51 116-1 3 1945

isolated The human body is unable to synthesize ascorbic acid in the necessary amounts and therefore has to rely on the plant sources especially the citrus fruits peppers green leafy vegetables tomatoes and other plant products

Vitamin C is easily *inactivated* by oxidation Cooking storing without refrigeration alkalization and the presence of copper even in traces rapidly diminish the content of active vitamin C In the organism it is concerned with the maintenance of connective tissue In scorbutic animal the *formation of fibers* from fibroblasts is seriously disturbed and the friability of the capillary walls which in clinical scurvy leads to many manifestations of hemorrhagic disease *may be explained by the lack of adequate intercellular substances* [97]

Scurvy is at the present time a rare disease In adults it is seen following malnutrition among inmates of ill managed prisons or other institutions in times of famine or after prolonged gastrointestinal disease with restricted diet Scurvy is more frequent in infants fed on cow s milk especially if the milk is being sterilized by boiling

In adults general weakness pains in the legs gingivitis purpura and other hemorrhagic symptoms are the classic manifestations Undeveloped cases are supposedly common and often mistaken for rheumatism [16, 1276] Infantile scurvy is clinically characterized by pallor a worried facial expression drawn up legs in bed crying when handled pains in the legs subperiosteal hemorrhages especially in the epiphyseal regions and gingivitis with bleeding if the child already has teeth Anorexia loss of weight susceptibility to infection fever intestinal disorders hematuria and epistaxis are other symptoms Urbach[16] considers the saturation test for vitamin A deficiency as much more valuable than *single determinations of the vitamin A content of blood plasma and urine* This test is based on the observation that the ascorbic acid levels in blood and urine fail to rise substantially and for considerable time in a vitamin A depleted organism after the intravenous injection of 500 mg of ascorbic acid In the normal 40 per cent of the injected vitamin is excreted within four hours while in scurvy the excretion is trifling 20 per cent at the most The diagnosis is helped by the positive tourniquet (Leede Rumpel) test or a similar method[1277] for testing the fragility of the capillaries Bleeding and coagulation times as well as blood platelet count are normal

The blood picture is normal except for a moderate anemia

The dermadromes of scurvy are significant though not specific The follicular slightly papular dull red hemorrhagic *rash* occurs early in the course of clinical scurvy Later many of these papules show pronounced intrafollicular keratosis The rash is symmetrical and occupies predominantly the extensor surfaces of the extremities particularly of the lower legs and the hairy region of the trunk The palms and soles the face and the scalp remain free [131, 137] Some of the follicular lesions are truly petechial without a papular character Large subcutaneous extravasations occur in the parts which are subject to friction and

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[1276] Eddy W H The Avitaminoses Baltimore 1937 Williams & Wilkins Co

[1277] Göthlin G F Method for Determining Strength of the Skin Capillaries Indirect Estimation of the Individual Vitamin C Standard J Lab & Clin Med 18 484-490 1933

trauma such as the popliteal areas and the scalp Extravasation beneath the conjunctivae also occurs These dermadromes are more common in infantile scurvy (Moller Barlow disease)

The papulo hemorrhagic keratotic and follicular rash in scurvy has for a long time been known under various other names like lichen scorbuticus [78] lichen pilaris or scorbutic gooseflesh [79] The First World War gave the opportunity for new observations of scurvy on a large scale In some series the papulokeratotic rash was present in 87 per cent [80] The follicular keratoses often affected almost all follicles especially of the anterior aspects of the legs so that a grater like surface resulted *Microscopic* features of the scorbutic skin lesions are capillary congestion interstitial hemorrhage and edema without inflammatory infiltrate The follicle contains a plug formed of the remnant of the hair and keratotic material The hair roots are not destroyed

The follicular lesions in scurvy (Whitfield after Wiltshire [80]) have much clinical resemblance to those in vitamin A deficiency However the vascular factor which is so pronounced in scurvy is lacking in phrynoderma Scheer and Keil [79] therefore believe that the follicular keratoses in scurvy are not due to a multiple deficiency In *experimental vitamin A* deficiency in man follicular keratotic papules and perifollicular petechiae were among the first symptoms [2, 81] Ecchymoses and gingivitis followed

Hyperpigmentation in scurvy has been observed [137] although it is not yet sure whether it is due only to hemosiderin from the hemorrhagic disease or also to the increased melanin production under the influence of vitamin C deficiency Ascorbic acid is able at least under experimental conditions to prevent melanin formation (von Szent Gyorgi after Schaaff [137]) In the human skin melanin occurs associated with vitamin C [13, 7]

Gingivitis in scurvy being an early signal is of great significance The gums are swollen and bleeding the papillae being enlarged In small children the teeth may become submerged under the swollen gingiva If the scurvy lasts longer the teeth may fall out and the alveolus may become necrotic It has often been stated that scorbutic gingivitis does not develop in an edentulous mouth

The *healing of wounds* is greatly impaired in scurvy [81, 8] at least in part due to the disturbed production of intercellular substances

Untreated and fully developed scurvy is a disease with a high mortality However if treatment with 200 300 mg of vitamin C is administered daily either orally or parenterally together with a full diet surprising recovery may be seen Cordon and Sevringhaus [207] state that in all the field of medicine there is probably no more dramatic or gratifying result from a therapeutic measure than that which occurs when a patient with scurvy is given an adequate amount of ascorbic acid

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[137] Jessner S Hautanomalien bei inneren Krankheiten Berlin 1893 A Hirschwald

[79] Scheer M and Keil H Follicular Lesions in Vitamin A and C Deficiencies Arch Dermat & Syph 30 177 18 1934

[80] Wiltshire H Hyperkeratoses of the Hair Follicles in Scurvy Lancet 2 564 1919

[8] Crandon J H Lund C C and Dill D B Experimental Human Scurvy New England J Med 223 353-360 1940

[81] Bartlett M K Jones C M and Ryan A E Vitamin C and Wound Healing Experimental Wound in Guinea Pigs New England J Med 226 469-473 194?

No relationship between the level of vitamin C in the blood and the development of a *variety of skin diseases* (altogether 181 cases) was found[2353] and no curative effect was noticed.[2354] Effects on *colloid milium*[2355] and on *toxicodermas* from arsphenamine,[2356] mercury,[2357] gold[2356] have been reported. Some evidence is available that vitamin C exerts a detoxifying influence on arsphenamine treatment and thus may be able to prevent toxic reactions.[2359]

[2353] Lever, W. F., and Talbott, J. H.: Role of Vitamin C in Cutaneous Diseases, Arch. Dermat. & Syph. 42: 657-663, 1940.
[2354] Hauser, I., and Braestrup, I.: Vitamin C and Skin Diseases, Acta dermat.-venereol. 20: 6-6, 1939. Abstr. Arch. Dermat. & Syph. 44: 263.
[2355] Way, S. C.: Colloid Millium a Vitamin Deficiency, Arch. Dermat. & Syph. 48: 1148-1155, 194
[2356] Dalnow, I.: Desensitizing Effect of l-Ascorbic Acid (Vitamin C): Curative Effect in Salvarsan and Gold Intolerance, Ann. de dermat. et syph. 6: 830-837, 193
[2357] Takahashi, S., and Sugai, M.: Klinisch Anwendung von Vitamin C gegen verschiedene Dermatosen, Jap. J. Dermat. & Urol. 42: 133, 193 (11: 88, 23).
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[2359] Lahiri, K. D.: Relation of Blood Ascorbic Acid Clearance to Arsenical Intolerance in Syphilotherapy, Brit. J. Dermat. 55: 158-159, 1943.

Chapter XXXII

DISORDERS OF THE BLOOD AND BLOOD FORMING ORGANS

(Lymphoblastomas and Allied Disorders)

Leukemia lymphosarcoma Hodgkin s disease mycosis fungoides and the subvarieties of these disorders are now—at least in America—commonly grouped together under the name of lymphoblastomas [2290] This term which is not much used in other countries is based on the conception that all these diseases have tumorlike features and that they are related by a common characteristic cell the lymphoblast or a derivative of this cell A great number of transitional cases have been described to corroborate the close relationship [2290, 2296] The neoplastic features are found in the continuous and uncontrolled proliferation of cells which tend to differentiate like their cells of origin The proliferation is infiltrating and is devoid of an orderly structural arrangement No cause is known The course is invariably fatal no certain phenomena of immunity or protection are known [2297, 2299] Heredity plays a role [2298]

Other authors [2300] produced some evidence for the infectious nature of the group Spread of the disease from a portal in the lymphatic tissues of the gastro intestinal and respiratory tract inflammation necrosis fever and some experimental facts can be interpreted in favor of an infectious possibly virus [2299] etiology Possibly in future a conception of infectious neoplasm will evolve

The term lymphoblastoma as a generic term has been accepted by authors who do not approve of the merging of the entities in question since they consider the differentiating characteristics of greater importance [2301]

Leukemia[2300, 2302, 2303]

Leukemia is a fatal disease of unknown etiology primarily involving the blood forming organs i e the bone marrow the spleen the lymphatic nodes

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[2290] Keim H L Lymphoblastomas Their Interrelationships Arch Dermat & Syph 19 533 534 1929

[2291] Krumbhaar E B Hodgkin s Disease Present Status University of Wisconsin Symposium on Blood pp 148 166 1939

[2292] Warthin A S Relationships of Hodgkin Disease Aleukemic and Leukemic Lymphoblastoma and Mycosis Fungoides Ann Surg 93 153 161 1931

[2293] Fraser J F Mycosis Fungoides as a Variety of Lymphosarcoma Arch Dermat & Syph 11 4 5-445 19 5

[2294] Fraser J F Mycosis Fungoides Its Relation to Leukemia and Lymphosarcoma Arch Dermat & Syph 12 814 8 8 19 5

[2295] Wile U J and Stiles F Jr Clinical Mutations of Lymphoblastomas J A M A 104 53 537 1935

[2296] Apitz K Die Leukämien als Neubildungen Virchows Arch f path Anat 299 1-69 1937

[2297] Mallory F B Principles of Pathologic Histology Philadelphia 1914 W B Saunders Co

[2298] Sly M Heredity of Leukemia (In Mice) Am J Cancer 15 1301 1346 1931

[2299] Keim H L Cutaneous Lymphoblastomas Clinics 3 866-885 1944

[2300] Forkner C E Leukemia and Allied Disorders New York 1938 The Macmillan Co

[2301] Ormsby O S and Finnerud C W Mycosis Fungoides Arch Dermat & Syph 27 631-64 1933

[2302] Haden R L Hematology Philadelphia 1939 Lea & Febiger

[2303] Rosenthal N and Harris W Leukemia Diagnosis and Treatment J A M A 104 702 706 1935

and the reticuloendothelial cells. It is characterized by widespread, rapid and disorderly proliferation of the white blood cells and their precursors. Almost without exception, either during the entire course or in some phase of the disease, the white blood count is high, sometimes very high. The appearance of immature leukocytes in the blood, often in very large numbers, is particularly significant. This proliferation of white cells almost always involves only one of the three types, the lymphocytes, the granulocytes or the monocytes. This is surprising considering the adjacency of the mother cells in the bone marrow and in other organs. The resulting three main types of leukemia, the lymphoid, the myeloid and the monocytic, are clinically quite different. Generalized enlargement of the lymph nodes is typical of lymphoid leukemia, but some lymphadenopathy may be present in the other types. The spleen is usually enlarged, the very large sizes being found in myeloid leukemia. In monocytic leukemia gangrenous and hemorrhagic lesions of the mucous membranes often dominate the picture. Weakness, dyspnea, fever and anemia occur in all types. A hemorrhagic tendency is an early and common feature in all types. The metabolic rate is frequently increased. In two out of three cases the disease takes a chronic course over years, with or without remissions. The acute disease ends fatally in a few weeks or months, often with hemorrhagic and mucosal symptoms. Acute course is known to occur in any of the three types. Approximately one half of the myelocytic and of the monocytic cases, but only one fourth of the lymphocytic cases, are acute.[23, 3]

The leukemias are relatively rare diseases. They constitute a little more than one half per cent of the necropsy diagnoses in a large American series (Ikeda after Forkner[300]), with about two cases of lymphoid leukemia to one case of myeloid leukemia. This ratio among the necropsies differs materially from that of hospital admissions. Among 455 cases of leukemia treated in Mount Sinai Hospital in New York, roughly 66 per cent were myeloid, 28 per cent lymphoid and 1.5 per cent monocytic. In Denmark roughly one out of 50 000 persons dies of leukemia per year (Nielsen after Forkner[2300]). No age is exempt, but the fourth decade of life has the largest incidence. The male patients outnumber the females two to one.[304]

Dermadromes Especially of Lymphatic Leukemia.—Cutaneous lesions occur in all types of leukemia. It is customary to distinguish between specific skin lesions, which histologically consist of the same cells which are characteristic of the blood in the case in question, and nonspecific dermatoses which are often seen in leukemia but do not contain leukemic elements.

The border line is not very sharp, since originally nonspecific lesions may finally become pervaded by the leukemic cells. Even grossly normal skin may prove to harbour specific infiltration. The nonspecific group is often called leukemids[30] or just ids. The term leukemid has become misleading since

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[23] Friedmann, A. B., and Meyer, L. M.: Observations on Over 100 Cases of Myelogenous and Lymphatic Leukemia, Radiology 44: 341-343, 1945.

[2304] Audry, C.: Sur les leucémides, Bull. Soc. franç. de dermat. et syph. 13: 118-121, 190

in analogy to the ids' in infections it suggests the specific and not the non specific type e g syphilids trichophytids etc (see discussion to Sweitzer[306]) The term 'accompanying dermatoses (Hautbegleiterscheinungen[1482]) has not found approval in the Anglo Saxon literature The adjective toxic has also been used to characterize these dermatoses It implies an etiology which has not been proved It seems best to speak of specific and nonspecific dermadromes There is no dermadrome which in a clinical sense is absolutely characteristic of one or the other types of leukemia The majority of published cases of skin lesions belongs to the chronic lymphoid leukemia[2307] However in an analysis of the cutaneous aspect of 160 cases of leukemia[308] the incidence was about equal in both main types Specific infiltrations were more common in lymphoid leukemia (8 3 versus 5 5 per cent) The cutaneous involvement in monocytic leukemia seems very high (75 per cent) but only small numbers are so far available The diagnostic difficulties in skin leukemia are considerably increased by the experience that the cases with leukemic skin manifestations are frequently subleukemic or aleukemic in the blood[307] They often show a leukemic blood only in late stages of the disease Another difficulty may be created by lymphocytomas These are infiltrations or tumors which histologically resemble leukemia but remain localized

Non-Specific Dermadromes —These are variable In their monograph Arzt and Fuhs[2309] mention dermatitis eczema erythema exudativum multiforme urticaria purpura and bullous and rupial eruptions This coincides with Nanta s remark that there are so many combinations in this group that if one would like to go into grouping every single observation could represent a type of its own The incidence is probably higher than fifty per cent minor skin lesions often passing unnoticed or at least unrecorded in the medical wards Pruritus for instance sometimes without any visible skin changes which seems to be the most common symptom, w is recorded only in three per cent of the leukemia cases of Epstein and MacEachern[2308] Most authors agree that severe itching alone or in connection with visible rashe is a frequent symptom[2309]

Purpura of varying degrees is also common in leukemia In large series[2307 308] it exceeds the other leukemic rashes This is not surprising in view of the thrombopenia and hemorrhagic tendency in the leukemias Chronic urticaria[2310 2313] has quite often been described It is related to Buschke s prurigo lymphatica This is a violently itching widespread not too dense eruption of small papules which soon become scratched and crusty or impetiginous The lesions may form

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[2307] Gottron H Zur Leukämie der Haut Med Klin 33 373-377 404-405 1937
[2308] Epst i E and MacEachern J Dermatologic Manifestations of the Lymphoblastoma Leukemia Group Arch Int Med 60 867 875 1937
[2309] Arzt L and Fuhs H Hauterkrankung n bei Leukosen und Leukoblastomen sowie verwandten Zuständen Handb d H u Gk 8 1 1929
[2310] Co nbleet T and Murphy E L Lymphatic Leukemia (Chroni) Leukemia Cutis Arch. D mat & Syph 36 643-645 193
[2311] Cavanaugh J M Lymph blastoma Arch D rmat & Syph 23 397 1931
[2312] Sehr in r C H Ein Fall von chronischer lymphatischer Leukämie ohne Milz oder Mandel geschwulst abe mit Urticaria. Med Rev 53 430-43 1936 Zbl 55 545
[2313] Orassi A Osservazion dieritema leucemico Arch ital di dermat sif 7 597-611 1931 Zbl 43 9

small erosions and ulcers which leave pigmented spots and streaks Thus a mottled melanoderma may ensue which resembles the so-called vagabond s skin The frequent lo s of body h ir in this stage is not only due to the rubbing off but also to a beginning specific infiltration around the hair follicles[2314] Total alopecia has been observed The histologic picture i as a rule not a typical leukemic one but surprising specific findings have become known demonstrating that there is no sharp borderline between the specific and nonspecific dermadromes[2315, 318] The same is true of the herpes zoster which occurs quite often in the course of leukemia[317] While the zoster may take a normal course its scars may later become the sites of pecific leukemic infiltrations[2316, 2] Such provocations of specific leukemic lesions by local inflammation or trauma interpreted as Koebner s phenomenon have been observed in many cases after local trauma like insect bites burns cupping piercing of the earlobe pinching of the ear and other local mechanical injuries[2] Aberrant or generalized zoster eruptions which are quite rare seem to occur more frequently in leukemia[2, 2] [2, 2] The rare connection of zoster and chicken pox in adults and also the varicelliform eruptions (H R Foerster in discussion to Barney[2, 2320]) have been ob erved several times in leukemic patients The generalization of zoster seems to occur especially in persons whose re istance has been weakened by disea e or age[461, 331] Evidence of involvement of the corre ponding spinal ganglion by hemorrhage or leukemic infiltration is on record[2] Som e of the zoster eruptions in leukemia may have been caused by arsenical

Specific Leukemic Dermadromes —Specific leukemic dermadromes appear in several types which notwithst inding their different clinical aspect have

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[2314]Santa A Les troubles l appareil hématopoïétiqu (Hématodermies) Nouvelle Pratique Dermatologiqu vol 5 pp 5 1 661

[331]Arzt L Leukämische Lymphomat s Zl l 49 5 7

[2] Bertaccini O Uber eine noch ni ht besch i ben Hauterscheinung (Rupia) im Verlaufe ein r chronischen Leukämi ch n Lymphad ose Dermat Wchnschr 98 741 48 1934

[317]Cra er L F and Haag r n C D A Note on the Occurrence of Herpes Zost r in Hodgkin s Di as Lymphosarcoma and th Leukemia Am J Ca) r 16 50 514 1932

[2] Ja las ohn J Haut Leukämi in Zo ter Resten Zl l 22 17

[2] Ja lassohn J H rpes Zost r und varicellenartig n Exanthem bei lymphatischer Leukämi Zl l 20 23

[2] Halle H Zo t r and Leukämi Pro okation l ukämisch r Infiltrate in der Haut Arch f Dermat u Syph 159 38 40 1930

[2] Lat F Zoster bei Leukämi A ch f De mat u Syph 161 561 61 193

[2] F rr ira Marques J H rpes zoster g ne ali atus b i Leukämie Arch f D rmat u Syph 176 95 308 1937

[2] Cotte u H and Ja ol t H Sul l ukämische Lymphad o is cuti na h H rpes Zoster g n e ali atus Zl l 32 548 1930

[2] Barn y R F L uk mia Cutis Resembling Herpes Zost r A h De mat & Syph 25 1150-1151 193

[2] Barn y R F Zo teriform L uk mia Cuti A h D rmat & Syph 37 238 46 1938

[2] Tara l O W a l Vogt H Zur Frag der Hautleukämi D utsches Arch f klin Me l 165 6 1940

[2] Haa k K Zoster g n ralisatus bei lymphatisch Leukämi De mat Wchns hr 95 1819 1820 193

[2320]Barton R L and O L a y I A Herpes Zo t r Ge erali atus Associated With Chronic Lymphatic Leuk mia A ch Dermat & Syph 51 263 65 1945

[461]Lutz W Skin Di ases in Relati n to General O ganism Review of Literature D rmatologi a 83 177 186 1941

[331]Philad lphy A and Ha lbofer I Varicell n b i leukämis her Lymphadenose Arch f Dermat u Syph 169 512 518 1934

[2] Freund H Zo t r und Leukämie Arch f Dermat u Syph 154 4 6-489 1928

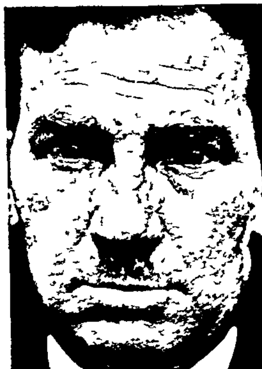


Fig 30 —Lymphati l uk mia Specific papular eruption (Co rt sy Dr M Jessner)

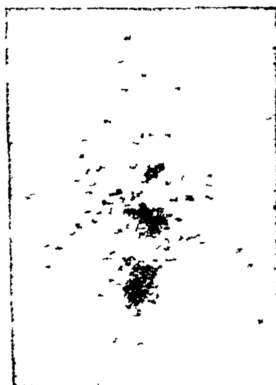


Fig 306 Lymphati leuk mia lich oi l eruptic (ourtesy D M Jessner)

a common histopathology the leukemic infiltration The rarest of the specific leukemic involvements of the skin is the generalized papular rash which has great similarity to a secondary syphilitic exanthema The dense[2309] eruption of small red mostly follicular papules favors the trunk especially the hips leaving the face and the limbs relatively free Considering its great rarity the diagnosis



Fig 307 Specific papular eruption in lymphatic leukemia (Courtesy Division of Dermatology Department of Medicine University of Chicago)

of leukemia will hardly be made from the rash alone But after exclusion of syphilis and other papular exanthemas e g drug eruptions leukemia should be considered[2312, 2313] This diagnosis will be much easier if the papules tend to coalesce and form plaques or if some papules reach tumor size Such cases of tumors arising from beds of papules link the papular type of cutaneous leukemia with the leukemic tumors Another transition is the furunculosis resembling rash of large not very distinct papules of moderately dense *distribution*[2314]

The *cutaneous tumors* in leukemia[2309, 2314] have been seen in sizes varying from a pinhead to a large potato They are oval or round mostly raised If they are

[2312]Arzt L Prurigo Lymphatica Zbl 54 71

[2313]Remenovsky Lymphatische Leukämie mit spezifisch papulösem Exanthem und bullöser Eruption Zbl 51 85

confluent the lines of coalescence are sometimes recognizable by deep linear grooves Their color may be red bluish, purple brown even almost black Under diascopic pressure they appear brown The skin over the tumors may be extended glossy atrophic with some telangiectases or scaly The tumors are usually movable The small tumors are quite hard The large growths are often described as soft less often as having the elastic hardness of cartilage The tendency to spontaneous regression either by central necrosis or healing with atrophy is small (Freudenthal after Gottron[307]) also[2 99] They are almost always painless The tumors may appear in any region of the body surface



Fig 308 — Lymphatic leukemic tumors (Courtesy Dr M Jessner)

but they have a definite affinity to the soft acra of the face i e the eyelids the lips the nose the cheeks and the ear lobes There is a certain tendency to symmetric development Such symmetric tumors may create the most grotesque disfigurement of the human face known to medicine In such rare but well known cases large bluish bulges hang over the eyes and cheeks obstructing the vision The nose resembles a proboscis the ear lobules may be pendulous and elongated In other cases the tumefaction is more diffuse over the face resulting in a facies leonina not unlike leprosy The scalp may also be involved The penis and praeputium sometimes become the site of leukemic tumors which may seriously interfere with micturition The nipples soft acra too have several times been described as a characteristic site of leukemic tumors[2334, 338]

Brecht P F Leukemia Arch Dermat & Syph 18 600 19 8
[338] Schildkraut J M Circumscribed Leukemia Cutis Arch Dermat & Syph 32 144 1935
Whitehouse My log nou Leukemia Arch Dermat & Syph 18 799-800 19 8

The mucous membranes of the mouth pharynx larynx nose and eyes may also become involved. Oral lesions *of this kind are described as nodular or* diffuse infiltrations. A picture of a patient of Milian's[2334] shows a lobulated gyrate tumor involving the whole soft palate and covered with petechiae. Such infiltrations of the soft palate have been seen several times.[2337] Connor describes a similar case in a Negro. There were large flat granulomatous masses practically covering the buccal surfaces on both sides. Smaller tumors were located on the soft palate and on the gums. The masses were dull red, the edges overhanging the bases sessile. There was some superficial ulceration in this case but the lack of ulceration is emphasized in other cases. In other instances[2338] the infiltrations were smooth and multiple scattered over the entire mucosa of *the upper air passages from the lips down to the larynx. In one case a tumor of* the epiglottis accompanied by skin tumors proved to be of lymphocytic origin.[2339]

Tumors have been observed in all ages including a seven months old baby,[2340] a three year old boy,[2341] and very old people.

The tumors often grow slowly or remain stationary over long periods, even as long as thirteen years.

In some cases the appearance[2341] of cutaneous tumors coincides with a change of a chronic course to an acute phase of leukemia with more numerous immature *cells in the blood.*[2342]

The diagnosis of the leukemic tumors is easy in fully developed cases. But difficulties which can only be overcome by repeated biopsies may arise if there is only one small nodule[2343] or if the lesion resembles other tumors, e.g. ulcerated epithelioma,[2344, 2345] melanoma,[2346, 2347] hemangioma[2348] or neurogenic sarcoma (author's case). Blood count and biopsy will finally assure the diagnosis but *it should be remembered that large tumors of the skin may be found in an* aleukemic phase of the disease.[2349]

Generalized Exfoliative Erythroderma. This complication of leukemia is very rare. Epstein and MacEachern[2305] saw one case in 60 cases of chronic lymphoid leukemia and not a single case in 90 cases of myeloid leukemia. It is about five times rarer than the other dermadromes of lymphoid leukemia.

[2337] Theodorescu S and Mal ter A Lymphatisch Leukämie mit Hauterscheinungen Zl 66 40 1938

[2338] Mar H Leucaemia cutis mit Beteiligung des Rachens und des Kehlkopfes Ztschr f Laryng Rhin 19 207 208 1930

McCafferty Lymphoma Arch Dermat & Syph 19 843 844 1929

[2339] Stalling S h at J B Ein Fall von Hauttumoren und myeloid Reaktion im Blut Nederl tijdschr geneesk 18 719 730 1930 Zbl 35 638

[2340] Simon H C Leukemia Cutis Proc Roy Soc Med 23 1031 1032 1930

[2341] Emile Weil P and Isch Wall P Les leucémies à tumeurs Sang 5 513-5 9 1931

[2342] Zeisler E P and Caro M R Lymphatic Leukemia of the Skin Arch Dermat & Syph 26 522 193

[2343] Buschke A Lymphatische Leukämie Zbl 41 294

[2345] White C J Leukemia Cutis Resembling Epithelioma Arch Dermat & Syph 26 5 1 193

[2346] Gray A M H Leukemia cutis Proc Roy Soc Med 23 1641 1642 1930

[2347] Rostenberg A Lymphatic Leukemia Arch Dermat & Syph 23 67 1931

[2348] Throne B Lymphatic Leukemia Arch Dermat & Syph 20 506 1929

[2349] Zimmerman F F and Curtis H C Aleukemic Myelosis With Cutaneous Nodules Arch Dermat & Syph 33 694-699 1936

The condition may precede the blood changes for years [350] or it may develop in any stage of the leukemic process It may develop secondarily to a specific papular rash or specific nodules [351 35] or nodules or tumors may follow the diffu e reddening of the skin [353] *In other cases the universal involvement of the skin* was ushered in by swelling and erythema of some regions mostly the groin and armpits [354 355] or by bullous eruptions suggesting pemphigus [3 6] In some instances exces ive perspiration was an initial symptom [357] Pruritus was almost always severe and remained so throughout the cour e of the disea e The variety of pictures seen in the initial stage of the disorder is in remarkable contrast to the uniformity of the later stages

The entire body surface is red sometimes bright red sometimes dusky or purplish The skin is often thick and leathery hardly pliable While the small wrinkles are mostly flattened the large folds are the more deepened The loss of pliability expres es it elf in painful fissures especially on the hands The exfoliation varies from slight branny scaling to the shedding of large heets of dry epidermis In some ca es ve icles crusts and oozing create the impression of a generalized eczema Nodules or plaques are sometimes found in the ery*throderma* *The axillary and pubic hair is shed early or rubbed off the hair* of the bearded area and of the scalp follow [314 358 359] The ground off concave edges of the nails and their glossy surfaces tell of constant rubbing and scratching Later on they are often dystrophic thickened opaque brittle and discolored

The superficial lymphatic nodes are all swollen the lack of axillary and pubic hair making them more visible The patient is very uncomfortable The rhagades the pruritus the ectropion which usually develops complicating pyodermic infections chilliness and the weakness and depres ion cau ed by the evere disea e create a horrible syndrome of suffering The course may drag on over many years In the later stages the infiltrated skin may become atrophic [358] Leukemic erythroderma is usually not influenced by any treatment including radiation

The fatal outcome is frequently precipitated by bronchopneumonia

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[350] Covisa J S and Pri to J G Erythrodermische Form der al ukämisch n Myelose Actas d rmo-sif 19 16- 2 256 1927 Zbl 32 76

[351] Pollmann J E ythrod rma l ura ml um aus hronisch r lymphoid r Leukämie mit knötch n na h Röntg nbestrahlung entwi kelt Orvosi hetil 77 394-397 1933 Zbl 45 469

[352] S olari E F ythrod rmia lymph ti a ex udativa l i kus Boll S z R gion Soc Ital Dermat pp 110-116 193

[353] Balina L an l D Ma val L Leber i en Fall von Erythrodermi und akuter lymphatis h r Le kämi D rmat Wchnsch 1930 II 11 0 1157

[354] Mich lson H E Leuk mia Cutis Arch D rmat & Syph 22 148 149 1930

[355] McCarthy F I Raynau l s Di as (Possibly Du to Chronic Ars nic I oiso ing) Arch D rmat & Syph 23 78 788 1931

[356] Margarot J Rimbaud P and Roch J Erythrode mi con titua it la manifestation cliniqu initial et pendant qu lque temps clusive d un leucémie a élém nt primo tiaux t d évolution ub-aigu Bull Soc f anc de d rmat t syph 42 1503 1510 193

[357] Ma Corma H Leuka mic F ythrodermia Proc Roy Soc Med 21 1171 1174 19 8

[358] Arnov J sl 3 Chro *ische lymphatisch Leukämie mit Lymphomato de Haut* & b Arch f d ges Med 30 412-417 1928 Zbl 28 280

[359] Theodorescou S Su n cas d éritrodermi leucémique Bull Soc roum Dermat 1 61-64 1929 Zbl 31 33

Chronic Myeloid Leukemia—Skin manifestations of chronic myeloid leukemia being much rarer than those in lymphoid leukemia are not yet well enough known to insure a definite type Hardly more than fifty cases have been published All the dermadromes observed in chronic lymphatic leukemia have been seen in the chronic myeloid type too Nonspecific hemorrhagic[2359]



Fig 309



Fig 310

Fig 309—Chronic myeloid leukemia Specific cutaneous tumors (From Paul J T and Limarzi L R Arch Dermat 104)

Fig 310 Chronic myeloid leukemia (From Paul J T and Limarzi L R Arch Dermat 1042)

urticarial pruriginous rashes[2314 361] as well as infiltrations plaques[36] and tumors are known[363] The impression prevails that there is less tendency for the tumors to develop in the soft acra especially in those of the face The facies leonina which is so striking in some cases of lymphoid leukemia has not yet become known in myeloid leukemia The tumors seem to occur more frequently on the trunk[36 361] The extremities have only occasionally been found to be involved

[236] Martenstein H Multipl Hauthäm hagi n bei my loi cher Leukämi Zbl 55 98 1937
[2361] Nekam L Les manifestations cutanées de la l ucémi myél 11 chroniqu Bull Soc franç de dermat et syph 44 1236 1? 4 1937
[2362] Haden R L Leukemia Cutis (Myeloblastic) Arch Dermat & Syph 37 870-871 1938
[23] Paul J T and Lima zi R R Specific Cutan ous Lesio In Chronic Leukemi Arch Dermat & Syph 45 897 905 1942

(Aubertin s case in a picture shown by Nanta [314] Hollander [2354] and others) Telangiectases on and around the tumors are especially mentioned by various authors [309 2336]

There seems to be a more marked tendency to hemorrhage necrosis and ulceration in the myeloid tumors particularly in those of the mouth [365 366] than in the corresponding lymphoid lesions



Fig 311 – Chro ic myeloid leuk mia Sp cific infiltration su r u li g a weat gland (F om I aul J T and Limarzi L R Arch Derm t 1942)

Monocytic Leukemia —Monocytic leukemia [367] constitutes only a small fraction of the leukemias [2303 ,309 368] But it is likely that cutaneous and oral involvement is relatively frequent in this type (three out of four cases of the series of Epstein and MacEachern[2308])

While so far no specific clinical picture different from the other leukemic dermadromes has evolved the frequent occurrence of exfoliative dermatitis is remarkable Purpuric and bullous lesions are often encountered in early stages and so are indurated eczematoid plaques resembling the premycotic stages of

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[365]Holland r L Kastlin G J Lerman H H and Schmitt C L Myeloid Leukemia With Cutaneous M nifestations Arch D rmat & Syph 29 821 834 1934

[366]Richt r W Myeloisch Leukämi mit Hautm tastas unter d m Bilde eines Abscesses Zbl 44 372

[367]Gottron H Perakute My loblast nleukämie Zbl 39 405 1931 193

[2307]Schilli g V S lt n akut Leukämi formen Verha ll 37 Kong deutsch Ges inn Med Wiesbad n 19 5

[2308]Doan C A and Wiseman B K Monocyt Monocytosis and Monocytic Leukosis Ann Int Med 8 383-416 1934

mycosis fungoides[2369, 2370] Shotty papular[2371] nodular or tumorous discrete or coalescent eruptions have become known[2372] The lesions may be either superficial or deep seated creating sarcoid pictures Their development seems to be faster and their tendency to spontaneous regression more marked than in the other leukemic tumors Ulceration[2372] is considered ominous[2370] As in the other leukemias the cutaneous changes may precede accompany or follow the



Fig 31 —Mo ocyti l uk mia (Court sy Di ision of D rmatology D partm nt of Medici e University of Chicago)

blood changes The dermatological diagnosis of monocytic leukemia can only be established by biopsy and in connection with other clinical findings[3] since the cutaneous picture may resemble all other lymphoblastomas

[2369] Loveman A B Mo ocytic Leuk mia Cutis South M J 29 3 7-364 1936

[2370] Mo tgom ry H and Watkin C H F foliative D rmatitis as Manifestation of Monocytic Leukemia Schilling Mi nesota M d 21 636-641 1938

[2371] Mercer S T The D matosis of Mo ocytic Leukemia Arch Dermat & Syph 31 615-635 1935

[2372] Freeman H E and Kol t ky S Cutaneous L ions in Monocytic Leukemia 2 Cas Arch Dermat & Syph 40 218 240 1939

[2373] Lynch F W Cutaneous Lesio s Associate l With Monocytic Leukemia and Reticulo Endotheliosis Arch Dermat & Syph 34 775 790 1936

Chloroma —In contrast to the earlier literature chloroma is now considered a variant of myeloid leukemia originating from the marrow especially of the cranial bones and taking the course of a highly malignant tumor The name (green tumor) characterizes the green color of the lesions produced by a lipid probably iron containing substance Two main clinical types of chloroma occur[2374] In the juvenile cases a rapidly growing orbital tumor produces exophthalmus and finally profound proptosis Cranial tumefaction with a great variety of symptoms lymphadenopathy gross involvement of other bones and severe anemia follow In the much rarer adult type the course resembles acute leukemia complicated by gross bony involvement

Since the arrival of the modern methods of hematology myeloid leukemia has been found to be present almost constantly Autopsy reveals green foci of myeloid tissue throughout the body

Severe anemia with a green hue and petechial purpura and varying macular or papular rashes[109] and tumors[375] have been described mostly in children Dense nodular greenish rashes in adults are known Similar to other acute leukemias ulcerative gingivitis and easily bleeding infiltrations of the base of the tongue and of the tonsils occur In contrast to the oral lesions of other leukemias these lesions are green in color



Fig 313 —Fc hym ses in acute lymphatic leuk mia

Acute Leukemia —Acute leukemia occurs about half as often as chronic leukemia and four out of five acute cases belong to the myeloic type[2303] Acute leukemia[376] usually starts with enlarged tonsils stomatitis and/or upper respiratory infection of more than usual persistence and severity Hemorrhages from mucous membranes particularly of the nose and gums are an early symptom which persists throughout the disease Anemia develops rapidly Splenic

[2374] Kaul I F A Chloroma Arch I t Med 59 691 01 1937

[375] Morrison M Samwick A A a 1 Rubi t in R I Cong nital Leuk mia With Chloroma Am J Di Chil 58 33 -338 1939

[376] Fo kner C F Acut Especially Monocyti Leuc mias Ar h Int Med 53 1-34 1934

enlargement often causes abdominal tenderness Due to the increasing hemorrhagic diathesis bronchopneumonia or sepsis death ensues within four weeks or less in 60 per cent of the patients and within eight weeks in 84 per cent [2377] None of 113 cases lived longer than twenty six weeks

The white cells which dominate the blood picture with usually over eighty per cent are uniform and immature mostly myeloblasts less often lymphoblasts or monoblasts The blood platelets run low and the coagulation and bleeding times are prolonged The absolute number of leukocytes may be about normal Leukopenia is common in the early stages

Skin and Mucosal Manifestations – Forkner [34] emphasizes the importance of initial gingivitis as an aid in differentiation of the acute leukemias It is most marked and diffuse in monocytic leukemia Here it may extend to the pharynx usually causing ulceration and bleeding More than in the other types a diffuse cellulitis is apt to appear about the lesions causing tooth ache and painful acute inflammation in the deeper tissues of the face The patients are usually first seen by a dentist If teeth are extracted the bleeding is severe and sometimes fatal Deep necroses have followed such extractions Several authors emphasize the submerging of the teeth in the swollen pale pink soft and tender gums which bleed easily [2378-2380] The oral aspect sometimes resembles scurvy Besides the gingivitis gangrenous punched out ulcerations in the floor of the mouth occur The necrotic character of the leukemic infiltration may dominate the changes in the tonsils and the lymphoid tissues of Waldeyer s ring [367] Noma resembling pictures may ensue [2309, 2331]

The nonspecific as well as the specific skin manifestations in acute leukemia are essentially the same as in the chronic cases However the nonspecific eruptions seem to have a purpuric tendency and the specific leukemic lesions show a greater tendency to regressive changes like central softening ulceration necrosis and gangrene This is illustrated by the observations of severe necroses after minor operations performed on acutely leukemic patients The deep and wide necrosis after the application of a vesicant (Leube and Fleischer after Arzt and Fuhs [307]) belongs here too The morphology follows the familiar patterns of papular rashes [23] [236] nodules tumors plaques and erythroderma [2386]

[2377] Warren S L Acute Leukemia Am J M S 178 490 500 1929

[2378] FitzGerald L J Oral Lesions in Leukemias J Iowa M Soc 33 474-476 1943

[2379] Lastenack J G Abbott C A and Werrer R D Leukemic Gingivopathy Case of Acute Aleukemic Leukemia J Am Dent A 29 1133 1137 1942

[2380] Osgood E E Monocytic Leukemia Report of 6 Cases and Review of 127 Cases Arch Int Med 109 931 951 1937

[2381] Herz A Klinische Beobachtungen bei der Lymphogranulomatose Wien Arch f inn Med 24 437-454 1934

[2382] Kerl W Acute Myeloblasten Leukämie Zbl 54 7

[2383] Cohen I Cutaneous Tumors in Acute Myeloid Leukemia Nederl tijdsch v geneesk pp 1051 1053 1938 Zbl 54 1 2

[2384] Epstein T Fall von akuter aleukämischer lymphatischer Leukämie mit ausgebreiteter spezifischer Hautveränderung Festschr f Béla Entz pp 4 49 1928 Zbl 29 662 1929

[2385] Suldberg F Zur Klinik der Leukaemia cutis Venerol 7 33-37 1930 Zbl 36 909 1931

[2386] Zimmermann O Zur Kasuistik der Erythrämie mit Uebergang in Leukämie Klin Wchnschr 13 696 699 1934

The histology of leukemic lesions of the skin and mucous membranes is of marked uniformity There is a more or less dense infiltration of the superficial or deep layers of the cutis composed of the characteristic leucocytes The infiltrates often form perivascular sheaths but in fully developed lesions the accumulation of cells throughout the dermis is so dense that the perivascular arrangement disappears

Hodgkin's Disease

Lymphogranulomatosis (Paltauf and Sternberg)

Hodgkin s disease is a chronic disorder of the lymphatic system It starts in sixty five per cent of the cases with the painless enlargement of cervical lymph nodes Graduallv other groups and finally the entire lymphatic system including the spleen and often the liver become involved The enlarged lymph nodes may become large tumors which cause severe local symptoms especially in the mediastinum Chronic intermittent fever weakness loss of weight, cough edema diarrhea anemia and finally cachexia are the usual features The blood picture is not characteristic but anemia is common Eosinophilia is present in 20 per cent and leucocytosis is an occasional finding The course may be rapidly fatal or slowly progressive over one to rarely more than three years A few instances of survival for much more than ten years are known

The disease is most common in the third decade of life but no age or race is immune Three out of five cases are in men

Dermadromes —The incidence of skin manifestations in lymphogranulomatosis follows generally the pattern of the other lymphoblastomas There are nonspecific and specific dermadromes The former are common and the latter are rare

Nonspecific Cutaneous Manifestations —The large series vary in their observations on *pruritus* in Hodgkin s disease Thirty two per cent (Burnams after Baum[2387]) eighteen per cent [2388] six per cent[2389] and three per cent (Longcope after Baum[2387]) are some of the percentages Especially in France pruritus seems to be considered so common that lack of it prompted publication of three cases [2390] Pruritus is often an early symptom which may precede the lymphadenopathy by as long as two years [2391, 2392] High blood sugar or unexpected high urine sugar

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[2387] Baum P Atypical Cutaneous Symptoms in Lymphogranulomatosis Arch f Dermat u Syph 178 418-4 4 1938

[2388] Burger R E and Lehman E P 54 Cases of Hodgkin s Disease Arch Surg 43 839-949 1941

[2389] Oakey R S Jr Hodgkin s Disease 52 Cases Hahneman. Monthly 79 130-140 1944

[2390] Polnso R Zuccoli G and Recordier M Trois nouveaux cas d lymphogranulomatose malign sans prurit et sans éosinophilie Sang 3 550-554 1929

[2391] Ambler J V Hodgkin s Disease Arch Dermat & Syph 25 1149 1150 1932

[2392] Madden J F Gangrenous Herpes Zoster in Hodgkin s Disease Arch. Dermat & Syph 39 758 1939

enlargement often causes abdominal tenderness Due to the increasing hemorrhagic diathesis bronchopneumonia or sepsis death ensues within four weeks or less in 60 per cent of the patients and within eight weeks in 84 per cent [2377] None of 113 cases lived longer than twenty six weeks

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[2377] Warren S L Acute Leukemia Am J M Sc **178** 490 500 1929

[2378] FitzGerald L M Oral Lesions in Leukemias J Iowa M Soc **33** 4 4-4 6 1943

[2379] Pasternack J G Abbott C A and Werne R D Leukemic Gingivopathy Case of Acute Aleukemic Leukemia J Am Dent A **29** 1103 1107 1942

[2380] Osgood F E Monocytic Leukemia Report of 6 Cases and Review of 127 Cases Arch Int Med **109** 931 951 1937

[2381] Herz A Klinische Beobachtung bei der Lymphogranulomatose Wien Arch f inn Med **24** 427-451 1934

[2382] Kerl W Acute Myeloblasten Leukämi Zbl **54** 72

[2383] *Cohen I Cutaneous Tumors in Acute Myeloid Leukemia Ned tijdschr v geneesk* pp 1051 1053 1936 Zbl **54** 172

[2384] Epstein T Fall von akuter aleukämischer lymphatischer Leukämie mit ausgebreiteter spezifischer Hautveränderung Fest chr f Béla Fritz pp 4 -49 19 8 Zbl **29** 66 19 9

[2385] Suldberg F Zur Klinik der Leukaemia cutis Venerol 7 33-37 1930 Zbl **36** 09 1931

[2386] Zimmermann O Zur Kasuistik der Erythrämie mit Uebergang in Leukämie Klin Wchnschr **13** 696-699 1934

especially in children [398, 399] Desquamation and dryness [400, 401] without other characteristics of erythroderma as well as petechiae are often noticed Herpes zoster well known as a dermadrome in other lymphoblastomas occurs in lymphogranulomatosis too [339, 402]



Fig 315 —Hodgkin's disease No specific violently itching eruption Note deep scratches Subsided after x ray treatment of mediastinal and inguinal lymphatic nodes

Generalized exfoliative erythroderma may be nonspecific or specific or at first the former then the latter It occurs in all degrees of severity Its clinical

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[398] Feer W Lymphogranulom bei Kindern Jahrb f Kinderh 123 145 160 1929

[399] Schoenhof S Die Lymphogranulomatose der Haut Handb d Haut u Geschlechtskr 8 1 271 338 1929

[400] Poór F Lymphogranulomatose mit eigentümlichen Verhornungsstörungen der Haut Orvosi hetil 73 1210-1211 1929 Zbl 32 791

[401] Ronchese F Ichthyosiform Atrophy of Skin in Hodgkin's Disease Arch Dermat & Syph 47 778 781 1943

[402] Pendergrass E and Lancoast H K Herpes Zoster in Hodgkin's Disease Am J M Sc 168 326-333 1924

picture hardly differs from that in lymphoid leukemia[2107,2103 2111] Ichthyosiform keratosis has been observed[2193]

Edema is a feature in advanced Hodgkin s disease It may involve a vast area or the whole body and be part of the cachexia Of greater dermatological interest is the localized elephantiastic edema of the penis and scrotum[112] and of the hands and feet[2112] *Melanoderma may reach degrees which suggest* Addison s disease Such pigmentations have been observed in cases without preceding x ray or arsenic medication[114] Hodgkin s disease has several times been seen to develop following unusually heavy pigmentation from sunlight exposure[2115]

Specific Dermadromes —*Tumors and Ulcerations* —This group includes papular rashes as well as infiltrations and larger lesions which one would be more inclined to call tumors They are all o the same nature There is no need to form a separate group of lymphogranulomatous ulcerations of the skin since no ulceration occurs without a preceding tumor

Papular rashes consisting of more or less densely[1 8 119] placed cutaneous papules resemble in their clinical appearance those encountered in leukemia *They may develop from preceding prurigo lymphatica*[2119] *A difference may* perhaps be seen in the more pronounced regre sive tendency of the lesions Erosion ulceration and healing with scarification or central depression is com mon[2111 2120 21 1] The lesions may be situated in varying depths of the cutis and subcutis thus varying in color and palpability The rash mostly covers the trunk with a certain predilection for the sternal area In some cases the lesions are grouped together in circinate[111] or corymbiform arrangement (Bruus gaard after Schoenhof[399]) The number of such observations however is too

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[21] Schreiber Lymphogranulomatose Zbl 58 507 1938

[2 4]Loveman A B Cutaneous Manifestations of the Lymphoblastomas Hodgkin s Disease J A M A 104 1583 1586 1935

[2 05]Wigley J E M Hodgkin s Diseas With Erythrod rmia Proc Roy Soc Med 31 81 1938

[21 6]Bruck C Lymphogranulomatosis maligna mit eig nartig n Hautv ra nderungen Acta Dermat 20 593 1939

[7]Löhe *Universelle Erythrodermie bei Hodgkinscher Krankheit Zbl 42 563*

[2 8]Gouge ot H Blum I Oberli g and Fila cheff O Atrophi de l épiderme et du derme sup rficiel et des juamation intense générall ée de la peau (sans érythrod rmie) dues à une lympho-granulomatos atypique Arch dermat-syph Hôp St Louis 4 349 360 1932

[2 9]Tommasi L Pityria is rubra di H b a-Jada sohn in oggetto aff tto da linfogranulomatosi malig a di Sternb rg Paltauf Gior ital di dermat e sif 71 1240-1248 1930

[2110]Spi ca G Di un caso di li fogranuloma Paltauf Sternberg (Eritrodermia pitiriasica tipo Hebra) Poli linico (sez med) 26 385-403 19 9

T pp ine S Lymphog anulomatosis (Paltauf Sternberg) of Skin Arch f Dermat u Syph 181 7 0 700 1941

[11] an h z Covisa J and de la Cuesta L Elephantiasis of Penis and Scrotum in the Course of Malig ant Lymphogranulomatosis (Paltauf St rnberg) Actas dermo-sif 28 734 738 1936

[2113]Pasztay G Lymphogranulomatosis Zbl 44 261 193 1933

[2 14]Riehl G J Pigmenti rung bei Lymphogranulomatose (Paltauf Sternberg) Zbl 56 5 1937

[15]G aham Little E Lymphogranulomatosis Proc Roy Soc Med 25 1550 1932

[21] Swelt er S F and Winer L H Ulcerative Hodgkin s Dis ase Arch Dermat & Syph 51 2 9 236 1945

[2 7]Nobl G Juvenil tuberöse Lymphogranulomatose Wien klin Wchnschr 46 717 719 1933

[2 8]Bersack S R Cutan ous Hodgkin s Di ease With Te minal Blood Stream Spread J A M A 126 10 5 10 6 1944

[2 19]Re l Lymphogranulomatosis cutis Zbl 56 597 1937

[2120]Dittrich Lymphogranulomatose der Haut Zbl 41 669

[2121]Waugh Hodgkin s Disease Arch Dermat & Syph 21 125 1930



Fig 316



Fig 317



Fig 318

Fig 316 Papulo-nodular specific eruption in Hodgkin's disease

Fig 317 — Papulo-nodular specific eruption in Hodgkin's disease

Fig 318 — Hodgkin's disease Papulo-nodular specific eruption and transition in exfoliative erythroderma.

(From Berta R J A. M A.)

small to draw conclusions with regard to an infectious nature. The grouped lesions link with the cases with large tumors in small numbers. A large node or plaque may be surrounded by satellites.[2422, 2423] Such plaques may reach hand size or may cover half of the scalp or even half of the chest[2411] or one groin.[2411] These giant plaques are quite suggestive of Hodgkin's disease and are rarely found in other lymphoblastomas. Tumors of the face[241] and of the ear lobes,[2424] sometimes in symmetrical arrangement,[4] may create a facies leonina. Local trauma may be followed by development of tumors. The consistency of the tumors



Fig. 319 – Hodgkin's disease. Ulcerated cutaneous tumor of the anterior chest wall.

varies with the depth and the degree of regression and scarring. An uneven firmness is a frequent finding (Wirz after Schoenhof[399]). The color of these lesions is described as red to dirty yellowish and brown. Most describers emphasize the tendency to ulceration and sinus formation.[411] The whole giant tumor plaque may become an ulcer with undermined[410] or infiltrated edges leading to invasion of deeper structures, even bones.

[2422] Greenhouse, C. A., and Cornell, V. H.: Lymphoblastoma (Hodgkin's Disease) of the Scalp. Case. Arch. Dermat. & Syph. 29: 569-573, 1934.

[2423] Kirkland, R. R., and Montgomery, H.: Cutaneous Ulcerative Hodgkin's Disease. Proc. Staff Meet. Mayo Clin. 16: 124-128, 1941.

[241] Brain, R. J.: Hodgkin's Disease With Dermal and Subdermal Nodules and Purpura. Brit. J. Dermat. 42: 445-448, 1930.

[2425] Rulison, R. H.: Hodgkin's Disease of the Lymphatic System and of the Skin. Arch. Dermat. & Syph. 35: 1202-1203, 1937.

Sometimes underlying structures like lymphatic nodes are primarily involved and the skin is invaded later in a scrofuloderma like fashion[24 6 4 8]

Specific oral lesions seem to be rare[2411] Paltauf[24 9] suggested that the lymphatic tissues of Waldeyer s ring were the portal of infection but clinical oral or pharyngeal symptoms are very rare considering the frequency of cervical lymphomas Only a few cases of ulcerative tonsillitis followed by specific neck nodes have become known[430 431] The rarity of tonsillar lesions compared with the frequency of cervical lymph node involvement does not rule out the tonsils as portals of entry[91]

Infiltrations and aphthoid lesions of the tongue as well as buccal pigmentations[243] have been seen In one case the tongue and oral mucosa and the glans penis showed a patchy exfoliation without any other skin manifestations[2433]

Diagnosis and Histology—The diagnosis of cutaneous lymphogranulomatosis rests mainly on the diagnosis of systemic Hodgkin s disease and on the histological findings in lymph nodes and in the skin lesions The use of stained lymph node imprints on glass slides for the demonstration of characteristic cells has lately been recommended[416] The specific lesions consist of foci of dense cellular infiltration in the corium and in the subcutaneous tissues The infiltrate is made up of lymphoblasts small lymphocytes plasma cells fibroblasts epitheloids mast cells and granulocytes Among the latter eosinophiles are sometimes found in large number The most characteristic cell of the polymorphous granulation tissue is a large cell with much protoplasm and containing one or several deep staining nuclei These nuclei are usually large and rich in chromatin and contain nucleoli which stain deeply with eosin Less often the nuclei are pale (Sternberg after Schoenhof[399]) These are the so called Sternberg and Dorothy Reed giant cells They are irregularly scattered throughout the granulation tissue which suggests a process of chronic inflammation rather than neoplasm However transformation into true sarcoma occurs

Tappeiner[411] emphasizes the almost constant occurrence of lipid filled phagocytes (pseudoxanthoma cells)

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[24]Pi k W Lymph granulom Zl l 45 14

[25]Ftt n G D ou t P L Flor ntin P and Louyot P Ob ervation d un cas d *form cutanée* ulcéreuse d la lymphogranul matos maligne Bull et mém Soc Méd d hôp le P ris 49 1144 1148 1933

[2 8]S ear F F and C a o M R Ulce ati Hodgkin s Dis a of th Skin Arch D rmat & Syph 35 114 1 8 103

[24 9]Paltauf R U be di Eintrittspforte des Virus d Lymphogra ulomato Wien klin Wehn h 42 437-439 19 9

[430] Nicolas J Massia G and Rousset J Un cas d adénl éosinophiliq ie pru igén (maladie d Paltauf Sternberg) Bull Soc fra de de mat et syph 40 369-37 1933

[411]Zoltá S Eine It n Rach nverä derung bei Lymphogranulomat se Monatschr f Ohr nb 63 7 9 78 19 9

[407]Bach r F Lymphogranulomatose mit Haut rsch inung n Arcl f Dermat u Syph 135 31 50 1921

[2433]Sharlit H Hodgkin s Disease Su fac Lymphogranulomatosi Confined to th Oral and Penil Mucosa Case Arch D rmat & Syph 24 288-290 1931

small to draw conclusions with regard to an infectious nature The grouped lesions link with the cases with large tumors in small numbers A large node or plaque may be surrounded by satellites [2422-2423] Such plaques may reach hand size or may cover half of the scalp or even half of the chest[2424] or one groin [2425] *These giant plaques are quite suggestive of Hodgkin s disease and are rarely found* in other lymphoblastomas Tumors of the face[2424] and of the ear lobes [2421] sometimes in symmetrical arrangement [2425] may create a facies leonina Local trauma may be followed by development of tumors The consistency of the tumors



Fig 313 —Hodgkin s disease Ulcerated cutaneous tumor of the anterior chest wall

varies with the depth and the degree of regression and scarring An uneven firmness is a frequent finding (Wirz after Schoenhof [2399]) The color of these lesions is described as red to dirty yellowish and brown Most describers emphasize *the tendency to ulceration and sinus formation* [2421] *The whole giant* tumor plaque may become an ulcer with undermined [2410] or infiltrated edges leading to invasion of deeper structures even bones

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[2422]Greenhouse C A and Cornell V H Lymphoblastoma (Hodgkin s Disease) of the Scalp Case Arch Dermat & Syph 29 569 3 1934

[2423]Kierland R R and Montgomery H Cutaneous Ulcerative Hodgkin s Disease Proc Staff Meet Mayo Clin 16 124 1 8 1941

[2424]Brain R J Hodgkin s Disease With Dermal and Subdermal Nodules and Purpura Brit J *Dermat 42 445 448 1930*

[2425]Rulison R H Hodgkin s Disease of the Lymphatic System and of the Skin Arch Dermat & Syph 35 1202 1203 1937

nodules in the skin or in the subcutaneous tissue Their number may be very great [2309 2446 448] There is a definite tendency to spontaneous regression which is rarely found in metastases of other malignant tumors The metastatic nodules are occasionally seen in close proximity to the primarily involved lymph node [2308]

Sometimes mediastinal lymphosarcoma penetrates the chest wall and invades the skin Even such advanced lymphosarcoma may still be clinically curbed by x ray therapy The incidence of metastatic nodules in the skin is given as 5 per cent [99] and as 13 9 per cent of 122 cases [2360]

The diagnosis is usually assured by biopsy There is profuse proliferation of a single type of cell invasion of the capsule of the node and the neighboring tissues abundance of atypical lymphoid cells without notable endothelial and reticulum hyperplasia and lack of Sternberg Reed cells [449] Differentiation from other lymphoblastomas is not always possible [2449] The therapy is radiological and surgical

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[2 46] Riehl G Jr Hauterscheinungen b i aleukämisch r in Lymphosarkomato e überg hend r Lymphadenos Arch f Dermat & Syph 169 200 11 1933

[24 7] Ri bes Fall zur Diagno Zbl 45 11

[2448] Finsen Lymphosarcomato is Cutis Zbl 39 619

[244] Cohn S and Richt r M Modern Views on Ho igkin s Disea e M Rec 148 243 1938

Chapter XXXIII

DISORDERS OF THE BLOOD AND THE BLOOD FORMING ORGANS

Anemia[4720, 830]

The red blood cells are formed from endothelium in the red bone marrow They pass through various stages of development (megaloblast normoblast reticulocyte) before they are released into the blood stream Besides the material necessary for the development of all cells two specific substances are required for the normal development of erythrocytes iron for the formation of hemoglobin and the erythrocyte maturing factor (E M F) which is produced in the gastric mucosa and stored mainly in the liver After a life span of from two to six weeks the red cells die and their remnants are phagocytized by the reticulo endothelial cells in the spleen Eighty five per cent of the iron is used again and bilirubin the other end product is under normal conditions excreted by the liver

The function of the red cells is the transport of oxygen from the lungs to the tissues Anemia is a reduction below normal of the capacity of the blood to transport oxygen [303] It may result from too small numbers of functioning red cells or from deficiency in their function due especially to lack of hemoglobin The clinical forms and stages of anemia are mostly explained by the phase in which a damaging influence hits the growing or mature red cell For example in the case of anemia from massive hemorrhage the mature cells are reduced in number In the case of pernicious anemia the maturing of the red cells within the bone marrow is disturbed by a deficiency of the E M F and so they die to a large extent in the bone marrow only an insufficient number of immature cells being released The bilirubin left over from the hemoglobin of the masses of dead red cells increases the bile pigment in the blood and may cause icterus

Dermadromes —*Pallor* is seen in practically all anemias and is directly proportional to the loss of hemoglobin [665]

In *hypochromic anemia* (chlorosis) which is rare today the pallor sometimes takes on a slightly greenish tinge Capillaroscopy shows the capillaries in various types of severe anemia to be pale thin or even empty and filament like with the arterial and venous sections hardly discernible

The estimation of pallor from the face and the mucosae is often deceiving Duke advises a quick test compare the palms of the patient with those of a normal person The palms should be held at heart level The advantage of the test which supposedly is quite accurate is the independence of the palms to emotional erythema and light

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[845] Meulengracht E Some Etiological Factors in Pernicious Anemia A Symposium on the Blood and Blood Forming Organs Madison Wis 1939 the University of Wisconsin Press

Chevallier[4 1] enumerates the following dermatoses as occasionally seen in essential anemias Rhagades of the fingertips and lips smooth atrophic tongue and buccal mucosa pruritus vulvae precocious graying of the hair and intertriginous erythema Corroboration of these impressions is still lacking although a similar list which includes coilonychia is given by Simon[245]

Pernicious Anemia

Besides the pallor found in other anemias too a yellowish *discoloration* is characteristic of this disease It is caused by the increased content of bilirubin from prematurely destroyed red cells and to a lesser extent from other substances in the blood plasma The icteric index may be above ten normal is four to six The third factor which influences the color in pernicious anemia is pigmentation which though rarely may reach degrees which suggest Addison s disease The pigmentation is mostly described as diffuse sometimes it has a predilection for the trunk chest abdomen and the dorsa of the hands As in Addison s disease the creases folds or scars may be darker than the surrounding skin[453] Freckled or lentigo like spots have been seen within the diffuse melanoderma (Lennartz after Kaufmann[11 5]) Another similarity to Addison s disease is found in slate colored or brownish spots on the oral mucosa Not only may the symptoms of Addison s disease occur in pernicious anemia but even post mortem findings of adrenal atrophy are on record[112] Bogorad[2453] saw improvement of the pigmentation under cortin while liver therapy alone failed to change it Most authors suggest that the melanosis in pernicious anemia is a hemosiderosis derived from the blood but the histological evidence is scanty and not clear[454 2456] The possibility of arsenical melanosis must be considered since arsenic was and still is used in pernicious anemia Patients with pernicious anemia under treatment with liver extract are supposed to tan more readily than normal persons[4 5] In a very extensive case of cutaneous and mucosal pigmentation in pernicious anemia the author could not notice any effect of liver therapy on the pigmentation despite good response of all other symptoms Ulcers of the lower legs which are more often seen in other forms of severe anemia are very rare in pernicious anemia[457]

The symptom known as *Moller s or Hunter s glossitis* is of practical importance because it may precede all other complaints and the hematological findings

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[2451] Chevallie P Die Dermatos n der Anaemie Med Welt 10 120 1 2 1936

[2452] imon C An mie etc Paris méd 1 47 51 1939

[245] Bogorad A G Hyperpigm ntation of Skin in Bie mer s A iemia Klin med 18 94 95 1940 Zbl 29 104

[2454] equeira J H and Latton I N Case of Eryth odermia With Lymphocytosis Brit J D rmat 32 378 19 1

[2455] Gantenberg R Hautpigmentation und Hautreaktion bei perniziö r Anämie D utsche med Wchnschr 57 1574 1931

[2456] Schurany T Pigm ntl rungen der Haut bei perniziöser Anämie Arch f Dermat u Syph 121 746 761 1916

[2457] Lasch F B ingeschwüre bei perniziös r Anämie Deutsche med Wchnschr 65 377-378 1939

PLATE V

1 Pellagra. Erythema of dorsum manus. (Courtesy Wisconsin General Hospital.)

2 Scurvy. Gingivitis. (Courtesy Wisconsin General Hospital.)

3 Ecchymoses in acute lymphatic leukemia. (Patient of Dr. [illegible] Kay.)

4 Pernicious anemia, untreated. Acute glossitis involving mainly the edges. Filiform papillae are still present. Note ecchymosis.

5 Pernicious anemia. Pale slick tongue. Atrophy of papillae.

6 Erythema nodosum.








PLATE V

in pernicious anemia [458, 460] The condition starts with a burning sensation in the tongue and occasionally in other parts of the mouth The pain and sensitivity to acid hard food and smoking often comes in spells Sometimes articulation is hampered In some cases only burning is noticed and no visible changes develop but more often fiery red painful round or oblong erosions appear usually on the dorsum close to the tip The filiform papillae within the patches are at first swollen but soon thinned or absent the fungiform papillae are often swollen and red [459, 461] The tip and the edges occasionally also the adjacent parts of the dorsum of the tongue are involved but sometimes also the inside of the lips



A B

Fig 320 — A Pernicious anemia Subchronic changes The papillae filiformes have mostly disappeared B Pernicious anemia Atrophy of papillae

cheeks and the palate (Harris after O H Foerster [46]) From the distribution on the tongue a V or U shaped figure results with the opening directed toward the base of the tongue Many authors[667] emphasize the contrast of the fiery red lesions on the tongue to the pallor of the other parts of the oral mucosa while others say that the red areas are the healthy ones and the pale areas the changed ones [2463] These may represent later stages of development The initial erosion is later followed by atrophy of the papillae which results in a smooth surface In extreme cases the atrophy may involve the posterior part of the tongue and the

[2458] Mag r W Zur Kasuistik d r Glossitis bei perniziö r Anämie Monatschr f Ohrenh 66 315-319 1932

[459] Heyn W Möll sche Glossitis Hunter sche Zung und perniziöse Anämie D rmat Zt chr 47 132 19 6

[460] Hasselkus A Moell r sche Glossitis Diss B rlin 1931 Zt 1 39 783

[2461] Hunt r W Se erest Anaemias Th ir Infective Nature Diagnosis and Treatm t London 1909

[46] Foerst O H Dermatoses and Associ ted Diseases of th Mucosa J A M A 73 653 1919

[463] Zinsser E Hautkrankh iten u d Mundkrankh it n Möller sche (Hunt rsch) Glossitis Handb d H u Ok 14 1 111 1930

papillae vallatae Slight edema of the tongue with visible impressions of the teeth has often been noticed in the early stages (Hunter's[2161] "hacked edges")

Though most frequently seen in pernicious anemia, Moller Hunter's glossitis or similar conditions occur in other severe anemias (tropical and nontropical sprue, pellagra, alcoholism, tapeworm, etc.)[2164] The painful red erosions of Moller Hunter's glossitis should not be confused with the dry, round, sharply outlined "plaques fauchées," which are seen in syphilis, or with the harmless "plaques lisses," which consist of non-inflammatory round areas which are devoid of papillae These completely painless lesions are usually accidental findings The transitory character and the fast traveling over the dorsum within a few days are characteristic of the wandering rash of the tongue The restriction of a chronic inflammation to a diamond-shaped area in the center of the posterior tongue marks the rhombic median glossitis[165] Liver therapy relieves the glossitis in pernicious anemia and so it has become rather rare If the patient sticks his tongue out, anemic stripes appear which correspond to the contracted muscles (Arndt after Heyn[2159]) This sign is considered valuable in early diagnosis The tongue is hardly ever coated

Sickle Cell Anemia

This is a severe hereditary anemia which derives its name from the characteristic sickle- or spindle-shaped erythrocytes (drepanocytes) which occur in great numbers as do other bizarre forms of the red cells The disease has almost exclusively been seen in Negroes, in a few instances in Sicilians[166] Jaundice is almost always noticeable[2167]

Dermadromes.—Punched out, sometimes serpiginous, unilateral or bilateral, extremely chronic ulcers near the ankles are common in this anemia They were seen in twenty out of twenty-eight cases[2168] and in 55 out of 214 cases[2167] These ulcers often develop after minor injuries Poor circulation in the lower legs and the known tendency to thrombosis in sickle cell anemia probably are pathogenetic factors Priapism, which has repeatedly been seen in sickle cell anemia, also can be explained by thrombosis in the vascular system of the penis[2169]

Therapy of the ulcers should consist of nonirritating local medication and treatment of the underlying anemia

Similar leg ulcers have been seen in a considerable number of cases of *hemolytic anemia* (hemolytic jaundice) This is a hereditary anemia characterized by unusual spheroid shape of the erythrocytes These ulcers sometimes only heal

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[2164] Manson-Bahr, P H Glossitis and Vitamin B Complex in Pellagra, Sprue and Allied States Lancet 2 317-356 1940

[2165] Brocq and Pautrier Glossite losangique médiane Ann de dermat et syph 5 1 1914-1915

[2166] Greenwald, L, and Burrett, J B Sickle-cell Anemia in White Family Am J M Sc 199 768-774 1940

[2167] McCava, K, T H, and Nussbaum, C C Skin Manifestations of Sickle Cell Anemia Urol & Cutan Rev 46 194-200 194

[2168] Cummer, C L, and LaRocco, C G Ulcers of Legs in Sickle Cell Anemia Arch Dermat & Syph 42 1015-1039 1940

[2169] Getzoff, P I Priapism and Sickle Cell Anemia 3 Cases J Urol 48 407-411 194

after splenectomy [470, 474] The jaundice in hemolytic anemia supposedly does not itch as other types of icterus usually do [0]

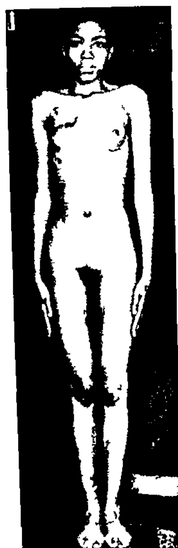


Fig 3 1 – Female aged 18 y ars Si kle ell an mia L g ulcer (From McGavack T H Urol & Cutan Rev 194)

[1 7] Taylor E S Chro ic Ulc r of th Leg Associated With Cong nital Hemolytic Jaundic J A M A 112 1574 1939

[t 1] E tape F d A Ulcus cruris y espl ectomia n l t ricea h molitica R v d cir B rcelona 1 447-459 1931

[7] Lau F J U terschenk lgeschwür bei hämolytisch m Ikterus Kli Wchns hr 10 409 410 1931

[1 7] E ppi ger H Schw r h ilbare Fussgeschwüre bei hämolyti chem Ikterus Klin Wchnschr 9 10-1 1930

[1] Lopp F Ein Fall von Icteru ha molyti u mit Untersch nkelgeschwüren Milz stirpa tion Norsk mag f laeg vi I nsk 95 05-710 1934 Z I 60 2 .

Hypochromic Anemia, Plummer-Vinson Syndrome —Dysphagia an atrophic oral mucosa anemia and often spoon nails or thin nails constitute a syndrome which does not seem to be rare Described by Vinson[2475] in 1922 as hysteric dysphagia but observed before it has been confirmed by reports from many countries It seems to occur more frequently in Sweden than in other countries[2476] The patients are almost exclusively women mostly in middle age Idiopathic hypochromic anemia with pallor but without jaundice is the most



Fig 3?2 —F mal aged 18 y ar S v re ickle cell a emia H moglobin 49 p r c nt R B C 1 66 million Hemolytic icterus Amenorrh a Ulcer of the lower l g exi ts for two years without any e-spo ise to tr atm nt It d v l p l after a dog bite (From McCava k T H Urol & Cutan Rev 194)

constant feature of the syndrome[2477] The red cells usually do not fall below 4 000 000 but the hemoglobin is reduced to 50 per cent or less Achlorhydria is seen in 75 to 90 per cent of the cases and moderate splenomegaly in

[2475] Vinson P P Hysterical Dysphagia Minnesota Med 5 107 19

[2476] *Ahlbom H E Achlorhyd ic Anemia Plumm r Vinson Syndrome a d Ca cinoma of the* Mouth Pharynx Esophagus in Women Brit M J 2 331 333 1936

[2477] Anderson N P Spoon Nail Anemia Cheilitis and Dysphag a Arch Dermat & Syph 37 816 822 1938

25 per cent Complaints of burning tongue especially after eating fruit and other acid food often lead the attention to the changes in the mucosa of the upper part of the gastrointestinal tract The patients have great difficulty in swallowing solid food so that their mealtime is prolonged

They soon arrive at a liquid or semiliquid often deficient diet

Dermadromes and Oral Manifestations —There is cheilitis varying from minor fissures to hypertrophic chronic inflammation or perleche Buccal leukoplakia occurs After a time the lips become thin and the mouth shrinks Ahlbom[24 6] who has given a very detailed description believes that the shrinking of the lips is part of the same atrophic process which leads to the changes in the tongue and esophagus Possibly the fact that these patients often lose their teeth early has some significance The surface of the tongue is described as glazed red dry smooth and devoid of papillae[2477 478]

There is much similarity to Hunter s glossitis but the involvement of the mucosa seems more widespread and more constant It not only involves the mouth but it extends to the upper—rarely the lower[30]—part of the esophagus Spastic or cicatricial stenosis of the mouth of the esophagus web formation across the lumen ulceration and other symptoms have been seen[478 2479] Cancer of the esophagus and multiple oral malignancies have been observed Especially in the relatively rare instances of cancer of the lip in women should the thought of anemia and Plummer Vinson s syndrome enter the mind[2478 477 2479] The post cricoid cancer of the esophagus which in 70 per cent to 90 per cent is encountered in women probably belongs here[476] Association of Plummer Vinson syndrome and kraurosis vulvae is also known (Rhoads after P Gross[2247])

Only recently after many cases of Plummer Vinson s syndrome have been described without mentioning coilonychia have spoon nails been discovered to form a rather frequent (about 70 per cent) dermadrome in hypochromic anemia[2307 476 47] The free edge of the nail is thin and sharp as if gnawed on The nail breaks or splits easily and in less complete cases the nail is only flat and thin It should not be forgotten that coilonychia may be produced by occupational factors e g work in soap suds and oils Dry gray pepper and salt hair are also mentioned in case reports[480] The similarity of Plummer Vinson s syndrome with ariboflavinosis has been emphasized[2481]

The treatment of the syndrome consists of administration of iron in liquid form hydrochloric acid riboflavin[2481] and bougieing of the upper esophagus which seems to be particularly helpful in relieving the dysphagia and facilitating a proper diet The oral as well as the nail changes are capable of complete restoration

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[2478] ?h r n J D Plummer Vinson Syndrome 2 Cases Arch Otolaryng 32 66 67 1940
[2479] G tlings P G Disorders of Mouth of Esophagus in Syndrome of Plummer Vinson (Dysphagia With Anemia J Laryng & Otol 55 143 153 1940
[2480] Dameshek W Primary Hypochromic Anemia J A M A 100 540 1933
[2481] Meulengracht E and Bick J J Riboflavin Avitaminosis and Plummer Vinson Syndrome Klin Wchnschr 20 831 834 1941

Granulopenia (Agranulocytosis)

Granulopenia [2432, 1463, 2433] is a deficiency of the blood in granulocytes caused by failure of the bone marrow to produce or release these cells It may be caused by toxic and allergic reactions [2434] to drugs such as arsphenamine trinitrophenol benzol amidopyrine sulfonamides and gold by radiant energy by infection and by allergic reaction [2434] Granulopenia also occurs secondarily to hyperplastic processes in pernicious anemia or leukemia Low leukocyte count—sometimes as low as fifty—acute sore throat exhaustion severe malaise fever and a moderate degree of icterus are in 50 per cent of the cases the manifestations of this dangerous disease The spleen is often enlarged Cases without any mucosal symptoms occur [1463] The red cell and platelet counts are essentially unaltered this accounts for the usual lack of hemorrhagic symptoms [2435, 2436, 2437] If they too are deficient (panmyelophthisis) hemorrhages occur [2433] The resistance to infections is extremely low The mortality in untreated cases was seventy-eight per cent in a large series Death may occur within thirty six hours from the apparent onset [2438]



Fig 323 —Agranulocytosis Ecchymosis

[2432] Hunter R J Agranulocytic Angina M Clin North America 22 1669 1681 1938
[1463] Marin A La granulopénie malig Union méd du Canada 69 126 2 0 359 469 1940.
[2434] Madison F W and Squier T L Agranulocytosis J A M A 102 755 759 1934
[2435] Clemens G Granulocytopenia in Lupus Erythematosus Dermat Wchnschr 109 1310 1313 1939
[2436] Jackson H Jr and Tighe T J C Treatment and Mortality of 390 Cases of Acute Agranulocytic Angina New England J Med 220 729 733 1939
[2437] Plum P Clinical and Experimental Investigations in Agranulocytosis London 1937 H K Lewis Co Ltd and Copenhagen 1937 Nyt Nordisk Forlag Arnold Busck
[2438] Staehelin R Agranulocytose und Panmyelophthise München med Wchnschr 85 1419 1423 1938

Oral Manifestation and Dermadromes —Angina is so much a part of the syndrome that the disease is often referred to as agranulocytic angina Bucco pharyngeal lesions are seen in 84 per cent [183] The soft palate uvula and anterior



Fig 3 4 —Agranulocytosis Ecchymoses (Courtesy Dr Erich Urbach)



Fig 3 Agranulocyto i ch ilitis and gingi itis Pati nt also ha l angina

pillars are red and eroded the redness being sharply bordered against the normal mucosa [219] The tonsil are enlarged and red sometimes with small white specks sometimes with severe ulcerations Ulcerations in other parts of the oral cavity and also in the nose [1] have been observed sometimes without involvement of

[199] R to B A Granulocytopeni With Peculiar Changes i Nasal Mu osa Monatschr f Oh enh 74 630-637 1940

the tonsils [2490] Gingivitis with adherent foul smelling pseudomembranes [491 492] is often present The gums bleed easily Rarely the ulcerations invade the bone or spread to the deeper tissues of the pharynx and larynx Edema of the glottis may necessitate tracheotomy [2493 493 494] Fusiform bacilli and large spirilla are commonly found The cervical lymph nodes are swollen but there is no generalized adenopathy



Fig 3 6 — Agranulocyto is du to di itrophenol poiso ing (Court y Dr Arthur I t k Sr)

The face is often cyanotic sometimes pallid or congested [497]

Cutaneous ulcerations about the body openings mainly around the mouth and nose were described by Landsberg [495] The e necrotic lesions are mostly small [482] but severe edema and lymphangitis may be present so that anthrax or other infections are simulated Cellulitis and deep noma like destructions are rare events Ulcerations in the neighborhood of the anus [496] or the genitalia [497] have been observed quite frequently [2493 498 500] Exanthems of erythematous pemphigoid vesicular papular or hemorrhagic [501] character and occasionally

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[2490] Béllard M and L bourg L Syndrome agranulocytaire à début buccal Guérison de l ulcération buccale Evolution vers un syndrome sub leucémique avec anémie pe ni l u Rev de tomatol 35 621-627 1933 Zbl 47 584

[2491] Dahmen Agranulocyto Zbl 48 354

Kruspe Disc Dahmen Zbl 41 559

[2493] Lothoven W J Bilaterale Laryn n krose bei Agranulocytose Arch f Ohrenh 147 196 1939 1940

[2494] Helsmoortel J Jr and Mulders M Agranulocytosis With Buccopharyng l Ma ifestations 2 Cases Ann d oto laryng pp 281 87 1940

[2495] Landsb rg M Hautverände ungen b i Ag anulozytose Med Klin 26 1 9 1 93 1930

[2496] Buck R W Agranulocytosis With Anal Ulcer J A M A 93 1468 1469 19 9

[2497] Reye E Ueber Haut und Schleimhautve änd rungen b i der Ag anul zyto e Dermat Wchnschr 89 1895 1899 19 9

[2498] Fortier L Agranulocytose nécrose cuta ée Union méd du Can da 61 940 0 1935

[2499] Greenbaum S S Acute Cutaneou Infection Associated With Agranulocyto i or Agranulemia Arch Dermat & Syph 28 135 136 1933

[2500] Dalous and Fabre J L s lé ions cutané s de l ag anulocyto e Arch d mal du coeur 27 645-656 1934

[2501] Allan W Agranulocytic Angina With Thrombopenic Purpura Ann Int Med 2 51 544 1928

typical erythema exsudativum multiforme have been recorded [48, 487, 500, 503] Marin [183] has seen giant herpes of the lips Pentnucleotide in large doses a stimulant for the production of leukocytes is considered helpful by many authors Otherwise the therapy is symptomatic Recently pyridoxin by intravenous injection has been recommended [04]

Polycythemia [30]

Compensatory increase of the erythrocytes (above 6 000 000 in men and above 5 500 000 in women) occurs under various suboxemic conditions e g low barometric pressures carbon monoxide poisoning and certain types of heart disease Such secondary increases of the red cells hardly ever exceed 8 000 000 Polycythemia vera is a disease of the bone marrow In this condition much higher sometimes enormous increases of the blood volume and of the red cells per cubic millimeter of blood occur The viscosity of the highly corpuscular blood of course is high After an asymptomatic phase which may last years cyanosis dizziness headache and quite often hepato splenomegaly develop Bleeding occurs from the nose and gums due to congestion rather than to a hemorrhagic tendency Variations of the normal syndrome include combinations of hypertension and especially in the final stages leukemia and anemia [0]

Dermadromes —The most common and at the same time most striking dermadrome of marked polycythemia is the *redness of the skin* This discoloration is most marked on the hands and face although in some cases it may be noticed over the entire body surface The shade and intensity of the erythema varies from a dusky purple cyanosis to a deep or in spots bright red Red as a rose in summer and blue as indigo in winter is descriptive of the changes under the influence of weather and temperature Osler [506] who used this description said that one of his patients was jokingly called the blue baby There is erythema in areas which usually do not take part in other erythemas e g the temples and the skin under the ears and between eye and nose The redness of the conjunctivae creates an impression of rage Contrary to congestion from other causes the redness stays constant during rest and sleep [507] While the erythema seems to be fairly even one can on close inspection and under glass pressure detect telangiectases on the red background This is particularly true of the mouth Capillaroscopy shows that the capillaries are dilated it is here and in the spleen where much of the excess blood is bottled up [08] Superficial telangiectases in the face often give the patient a ruddy complexion Besides

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[50] Cort r Ag anulocyt Ned rl tiji chr g esk p 37 4 1938 Zbl 61 52

[5] Ellman P a d Law c J S Agr nulo yto is With Pu pura Hemorrhagica Following Cold The apy I r ntion of Complications Brit M J 2 C 6 3 193

[2] Kn t n Tr atment of Leukop nia and Cr nulocytop nia With Pyridoxin Acta Med Scand 125 3 6 1946

[05] Rosenthal N and Bas F A Poly yth mi Course Arch Int M d 62 903 917 1938

[506] O l W Chroni Cyano i With Poly yth mia a d Enlarged Splee n N w Cli I al Entity M Classi s 4 1 7 1939

[507] D eck G a 1 D ckhorn E Poly ythe ia Med Klin 35 16 4 16 6 1939

[5] B onn C F a 1 h a d Ch Mea urem t o tl Skin Capillari s in Ca es of Poly yth mia Ver Rôle of the Capillaries I th I oduction f E ytl rosi J Clin In estigation 2 4 3 19 6

linear telangiectases small deep cherry red papular hemangiomas are known to occur in polycythemia

The color of the *oral mucosa* is deep cherry red Relatively early in the course of the disease the soft palate may appear considerably redder than the hard palate so that the borderline is marked [93] In the cyanotic stage the tongue is swollen deep purple and the papillae atrophic Bleeding from the blood gorged gums occurs but is slight since there is no hemorrhagic tendency [2510 2511]

Small pigmented spots are often scattered over the reddened areas They are probably due to hemosiderin deposits after small hemorrhages

Telangiectases and petechiae constitute the elements of *purpura annularis telangiectodes* a dermatosis which has been found to be a dermadrome of a considerable number of milder cases of polycythemia [2512 2513] Without preceding hyperemia or infiltration small lavender to purplish colored spots appear These maculae consist of capillarectases and petechiae The lesions appear in crops They often start in a follicle and spread peripherally leaving a slightly atrophic scar and resulting in rings [514] and polycyclic figures

The tourniquet test is usually negative

The viscosity of the blood the high platelet content the large blood volume and the high blood pressure favor a variety of *vascular disturbances*

Thrombosis has been observed in many organs and is together with arteritis responsible for gangrene ranging in severity from the blistering of a toe to the loss of an extremity [2511–2515] Various *ulcerations* of the lower legs have been observed [2516 518] Circulatory disturbances account also for the many instances of paresthesias Raynaud like symptoms and transitory painful red warm areas similar to erythromelalgia [2511 519 2520] Norman and Allen [521] reporting on ninety eight cases of polycythemia mention arterial disease in 33 per cent

Rosacea in polycythemia has been described several times although some of the cases had better be grouped with *acne urticata* a relatively rare dermadrome of polycythemia *Acne urticata* is a chronic itching dermatosis which resembles prurigo quite closely It starts on the face but has a tendency to involve the back and the extensor surfaces It develops from an urticarial papule with a

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Kup rman D J Symptomatology of Frythremia Vestn Otol i t d 2 210 215 1037 Zbl 57 466

[2] Ssutej G Skin Cha ges and Pathogenesi of Vaqu z Di ase Venerologia i d rmatologija pp 744 755 1926 Zbl 23 672

[2] Ssut j v Skin Changes in Erythr mia Zbl 26 37 1928

[2] Gott o H Purpu a Majocchii A ch f De mat u Syph 159 355 1929

[2 1] Brüna r St Pu pura annulari t leangiectode Majocchi Zbl 38 587 1931

W inma n H Haut eränderungen bei Poly yth mia ul ra Dis E lang n 1937

[2515] Beck r F Ext mitäte k o e b i Polycythaemia vera Klin W hnschr 11 1260 1 6 1932

[2516] Tbl m Trophoneu oti ches Ulcus Zbl 25 766

[2 17] Z lte W J Peripheral Vascular Disturba s in Poly ythemia M Clin North Am ica 24 485-492 1940

[51] Hallam Ulcerat i Nodules on L gs As o iated With Sple omegalic Polycytha mia B it J De mat 42 92 93 1930

[25] Grjas v F Ein Fall iner kombiniert n Erkrankung vo Eryth omelalgie u d Polycythämi Russk Klin 11 28 35 19 9 Zbl 52 8

[25] Gans O Poly yth mia Ve a Vi chows Ar h f path An t 263 565 573 1937 Zbl 21 62

[2 21] Norman I L and Allen E V Vascular Complications of Polycythemia Am Heart J 13 257 274 1937

central vesicle which soon becomes excoriated The crust covered lesion may ulcerate and heal with a pigmented scar Crops of new lesions follow each other The condition has much similarity to prurigo lymphatica which occurs in leukemia Thus acne urticata represents another link to leukemia which not infrequently constitutes the final stage of polycythemia [5]

The treatment of polycythemia is to remove or destroy the excess of erythrocytes by blood letting irradiation phenylhydrazine arsenic and other drugs

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[25] [2]Weidman F D and Klauder J V Acne Urticata Polcythaemica Positive Oxydase Reaction in Lesions Macroscopically and Microscopically Arch Dermat & Syph 39 645-666 1939

CHAPTER XXXIV

DISORDERS OF THE BLOOD AND THE BLOOD FORMING ORGANS

Hemorrhagic Diseases

The characteristic common to all diseases of the hemorrhagic group is abnormal bleeding. The flow of blood from an injured vessel starts a sequence of mechanisms. The injured small blood vessel contracts slowing down or stopping the bleeding. Macfarlane [23] explains this primary vascular constriction by assuming that the flow of blood removes the dilating histamin like substance released by trauma. Blood platelets then form a clot which is finally reinforced by the formation of fibrin. The vasoconstriction is a quick response which slows the flow of blood sufficiently so that the platelets can collect from the blood and form an adherent thrombus. This clot retracts and closes the wound firmly and permanently. Since the contracted vessels relax after a certain period of time blood would start flowing again and the clot would be pressed out if it had not become firmly adherent and by its power of retraction pulled the walls of the injured vessel together [390] [illegible]. This mechanism of hemostasis may be disturbed in any of its phases. There may be lack of capillary reaction, clotting may fail or a combination of both may occur. *Abnormal bleeding will result in any case.* Furthermore decreased resistance of the capillary wall is an important factor in many hemorrhagic diseases.

In thrombocytopenic purpura lack of capillary contractility and a low platelet count are combined. The bleeding time is prolonged just as it is in athrombocytopenic purpura where the platelet count is normal. In Osler's disease the trouble is completely vascular and restricted to the capillaries. In hemophilia, fibrinopenia, pseudohemophilia, jaundice and hemorrhagic disease of the newborn defective coagulation is responsible, in the two latter conditions being combined with capillary dysfunction [illegible].

Capillaroscopic observations [illegible] suggest that the blood of ecchymoses does not come from the capillaries but from the subpapillary venous plexus. Fresh petechiae have a red color. This is probably due to the presence of engorged very superficial small vessels and a small amount of extravasated blood in the upper layers of the cutis. The combination of vasodilatation and free hemorrhage in the deeper layers produces a bluish lesion [illegible].

Blood Coagulation – The transformation of fibrinogen, a labile colloidal blood protein which is probably formed in the liver or perhaps in the reticulo

[illegible] Macfarlane R G Mechanism of Hemostasis Quart J Med 10 1 29 1941

[illegible] [illegible] Capillarmikroskopische Beobachtungen bei Purpura Deutsches Arch f klin Med 175 534 [illegible] 1933 Zbl 47 479

[illegible] Peck S M Rosenthal N and Erf L Purpura Classification and Treatment With Special Reference to Treatment With Snake Venom Arch Dermat & Syph 35 831 867 193[illegible]

endothelial system into fibrin of which the clot mainly consists is only the final phase of the chain of reactions which constitute coagulation The formation of fibrin from fibrinogen needs an enzyme thrombin which is not present in the circulating blood since the blood would otherwise coagulate in the vessels If needed it is synthesized from a liver protein called prothrombin and free calcium ions Naturally the prothrombin too must be held inactive under normal conditions The activator of the prothrombin is thromboplastin which is held ready in the blood platelets

The most important methods used to diagnose a hemorrhagic disease are [890 302]

1 The *coagulation time* of the blood Normal blood coagulates in a test tube in one to five to eight minutes (Lee and White)

2 The *bleeding time* The skin bleeds from a small cut into the ear lobe for from one to three minutes The bleeding is recorded by blotting on white blotter every thirty seconds (Duke s method) This demonstrates the capillary reaction to injury

3 The *capillary resistance* This is most readily tested by the *tourniquet test* (Leede Rumpel test) Haden [30] calls the test positive if after placing a blood pressure cuff on the upper arm for three minutes at a pressure of 100 mm of Hg a crop of petechiae appears below and under the cuff According to Quick[890] the pressure should be kept for eight minutes midway between the diastolic and systolic pressures The petechiae which are visible to the naked eye within a circle 5 cm in diameter drawn on the flexor surface of the forearm with the center 4 cm below the bend of the elbow are counted after fifteen minutes The test is considered positive if more than ten petechiae appear Other tests for capillary fragility based on pinching [-6 2 7] suction [167 25 8 2530] or perfrigeration with ethyl chloride [531] have not become as widely used as the simple tourniquet test Madison and Squier [53] and many other investigators consider a positive Leede Rumpel test a pathological finding of significance These authors found the test positive in scurvy severe infections malignant hypertension ovarian dysfunction allergic reactions in the final phase of some malignancies and especially in primary blood diseases Intradermal injection of 0 1 or 0 2 c c of a 1 3000 solution of dried moccasin venom is another method for gauging the capillary resistance [2525] The test is positive when a hemorrhage of 1 cm or more in diameter appears within one hour at the site of injection

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[2529] Koschewnikow P W Z Frage d Brüchigkeit der Blutgefässe d r Haut Arch f Dermat u Syph 167 448-460 1933

[2 7] Hamm F Hämorrhagische Krankheiten Handb d Haut u Gk 6 2 512 83 1929

[2528] von Borbély F Ueber die Blutungsbereitschaft der Haut München med Wchnschr 77 886-888 1930

[25] Fromyer E Allgemeine Dermatologie oder Pathologie der Hautkrankheiten Berlin 1896 Gebrüder Borntraeger

[2530] Cutter J S and Johnson C H Capillary Fragility A Device for the Study of Capillary Hemorrhage J A M A 105 505 1935

[531] Brreaglia A New Sign of Capillary Fragility Elicited by Ethyl Chloride Perfrigeration in Case of Orthostatic Purpura Riv di clin med 41 263 271 1940 Zbl 30 318

[53] Madison F W and Squier T L Bleeding Due to Capillary Defect Wisconsin M J 39 31-34 1940

4 *Clot retraction time* The clot normally separates from the serum in thirty to sixty minutes If the platelet count is lower than 70 000 no or incomplete clot retraction occurs

5 *The platelet count* The normal platelet count is 250 500 000

These relatively simple tests are sufficient for the vast majority of cases For chemical assays of blood components which participate in the process of coagulation see Quick [890]

Hemophilia

Hemophilia is a hereditary constitutional lifelong disease characterized by severe bleeding on relatively slight trauma It becomes manifest only in the male although the daughters of a patient are able to transmit the disorder to their sons Besides dangerous and often fatal hemorrhages following injuries hemorrhages into body cavities especially joints are common while spontaneous hemorrhages into and from the mucous membranes do not belong to the typical syndrome Lasting deformities from hemarthrosis are usually present after the age of ten [2533]

The typical laboratory findings in hemophilia are prolonged coagulation time sometimes of more than 48 hours while the platelet count the clot retraction and the bleeding time (from puncture or small incision) are mostly normal It seems contradictory that the bleeding time from small cuts is normal according to most authors and that at the same time the blood needs so much time to coagulate This is explainable by the intact capillary constriction and by the fact that hemophilic blood still clots a little when passing over hemophilic tissue [890, 2533, 535]

The presently accepted explanation for the pathogenesis of hemophilia is the resistance of the platelets to disintegrate and to release the thromboplastin This in turn prevents the release of the prothrombin which is needed for clotting Why the blood platelets are so resistant is unexplained [890] A vascular factor consisting of pathological vasodilatation on slight stimuli (Ricker after Gottron[2131]) may play a part

Dermadromes —In contrast to other hemorrhagic diseases hemorrhagic skin lesions are not a dominant feature There are usually no petechiae and the tourniquet test is negative except during bleeding phases [535] The patients bruise more easily than normal persons and occasionally show large ecchymoses which require a long time to disappear [2131] Small bruises in hemophiliacs tend to have a hard raised blanched center surrounded by discoloration [2533] Such ring shaped suffusions may become concentric rings if the central bleeding recurs If it stops the periphery may continue to extend into the surrounding tissues Large hematomas of the scalp are often seen It has already been mentioned that small skin wounds do not bleed excessively Even minor operations like lancing

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[2533] Birch C L Hemophilia Illinois Medical and Dental Monographs No 4 University of Illinois 1937

[2131] Émile-Weil P Hémophilie Nouveau traité de médecin Publié par G H Roger Fernand Widal and P J Teissier vol IX Paris 1927 Masson & Cie

[2535] Bulloch and Fildes Hemophilia Treasury of Human Inheritance Galton Laboratory University of London Part V and VI Sec XIVa London 1911 Cambridge University Press

of an abscess have been done without excessive bleeding However circumcision tooth extractions small furuncles vaccination pustules blows on the nose and biting of the tongue have often caused serious or fatal bleeding Small injuries in the mouth may develop constantly growing clots which fill the whole mouth and protrude like a huge tongue Similar growing clots can be seen on the skin A rare incident is dry gangrene of a foot with spontaneous amputation without bleeding as seen in the case of a boy [332]



Fig 3 7—Hemophilia A mall furuncle was followed by a depl ting hemorrhage which lasted f r five weeks The picture show th crust eight weeks later (Courtesy Dr G L Birch and Uni v rsity of Illinois Press Monog aph on Hemophilia)

According to some older authors the hemorrhagic tendency decreases in the adult age but the majority of the hemophiliacs bleed to death in childhood *sometimes at birth from the umbilical cord* More recently the decrease of the hemophilic tendency in advanced age has been denied [333] Periods of in

creased hemorrhagic tendency sometimes alternate with almost normal periods Spontaneous hemorrhages frequently recur in cycles of three to six weeks Spontaneous hemorrhages have occurred in the early spring less severe ones in the



Fig 3 s —Hemophilia Th pati nt suff r d a s nall cut in the mucou membrane of the lip A day later h l ga to ble l and continu l for ight days Th welling of the lip and th larg clot made it impos it l fo the pati nt to at so that he ha l to b f d liqu d through a yri ge i serted into his mouth and di ected tow d th hard palate Th pas age of a nasal tube i a d ng rous proc dur in a h mophiliac (Cou tesy Dr G L Birch and Univer ity of Illinois I r ss Monograph on H mophilia)

fall Hemorrhages may continue for days and weeks with tremendous loss of blood The immunity of women is probably not an absolute one since a hemorrhagic tendency especially from the uterus has been claimed in some females [534]

Émile Weil Opitz and Zweig after Gottron [131] see review of older evidence in Bulloch and Fildes) [2535] Birch[2533] gives a long list of bleeding females of hemophilic families but she considers none of them as a true case of hemophilia

No effective treatment of hemophilia is known but injections of blood plasma human and animal serum and human placental extract may tide the patient over a critical period Several substances have been prepared from blood

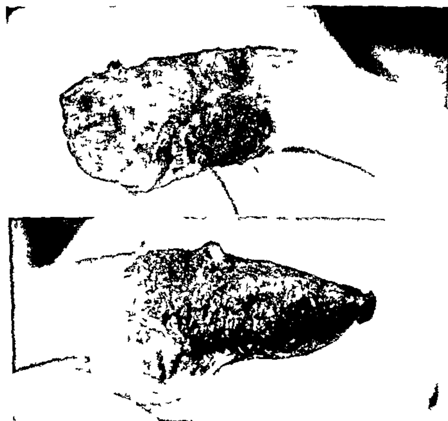


Fig 3 9 — Hemophilia Gangrene of the foot which followed an extensive [illegible] the right lower abdominal wall and the entire right leg The foot was later [illegible] without the loss of a single drop of blood (Courtesy Dr C L Birch and University [illegible] Monograph on Hemophilia)

and plasma which are able to decrease the clotting time of [illegible] Nateina Llopis a vegetable vitamin and calcium phospha[illegible] praised has been little heard of during the last fifteen years Many [illegible] have had the same fate Pressure applied to a wound tends [illegible] rounding subcutaneous hemorrhage [533] Several hereditary [illegible] resembling true hemophilia but differing either in heredity or [illegible] clinically ings have been described They are all of little dermatol[illegible] find

Pseudohemophilia is a rare hereditary disease which unlike true hemophilia occurs in and is transmitted by both sexes The disease may be carried with out manifestation

The symptoms are like those of hemophilia but mostly milder especially later in life The condition may disappear as the patient grows older Epistaxis easy bruising and ecchymoses are common but purpura and petechiae have not been seen[2,38] Macfarlane[2] has shown in capillaroscopic photography that



Fig 330 —Hemophilia Extensiv hemorrhag aft r a tiny furuncle of the right cheek (Courtesy Dr G L Birch and U iversity of Illinois Press Monograph on Hemophilia)

the capillary loops are partly distorted and do not retract after puncture so that bleeding continues in spite of normal blood platelets coagulation time clot retraction and tourniquet test The bleeding time is prolonged

Hereditary (familial) purpura simplex is much more common than hemo philia It is more often found in women than in men The platelet counts the bleeding coagulation and clot retraction times are mostly normal but the

[238]Minot G R A Familial Hemorrhagic Co dition Associated With Prolongation of th Bleed ing Time Am J M Sc 175 301 19 8

tourniquet tests are often positive [537 2541] The skin manifestations are mainly spontaneous ecchymoses

In *afibrinogenemia* (pseudohemophilia of the German literature) [54 2541] an extremely rare anomaly characterized by lack of fibrinogen in the blood all hemorrhagic symptoms of hemophilia including fatal hemorrhage may occur Coinsized ecchymoses around the big joints have been noticed and the patients bruise easily The blood does not coagulate except on addition of fibrinogen [444]

Osler's Disease

Rendu Osler Weber s disease is a well defined syndrome which is also known as angiomatosis hereditaria hemorrhagica

H I Goldstein [545] showed in a series of analyses of the accumulated material that up to 1931 about 110 families had become known in which more than 650 cases of the syndrome occurred Since then the number of published cases has become larger There is much discussion about the priority since many cases belonging to the condition had been published before Osler who recognized the triad of telangiectasis hemorrhage and heredity [2546]

The first visible telangiectases hardly appear before the age of twenty They appear in crops with a certain predilection to the cheeks and lips Since the individual lesions rarely disappear spontaneously their number grows with the age of the patient and may reach several hundred

There are several types of telangiectases Some of the smaller ones show pulsation under weak glass pressure but most of them are venous [547 2548] There are also small red hemangioma like papules with or without surrounding dendritic vessels These lesions cannot be blanched by pressure

The telangiectases develop on the mucous membranes too The nasal cavity the tongue and the gums are almost always involved Hemorrhages have been observed from almost all mucosae from the vagina the uterus the bladder the rectum and other parts of the colon from the stomach the bronchi and the larynx but the nasal septum is by far the commonest source of dangerous

[2537] Witts L J Th Hereditary Ha morrhagic Diathesis Guy s Hosp Rep 82 465-474 1932

[2538] Davis E H reditary Familial Purpura Simpl x Lanc t 1939 2 1110-1114

[2539] D vis E H editary Familial Purpura Simplex R view of 27 Families Lanc t 1941 1 145-146

[2540] Bailey F R and M Alpi K R Familial Purpura R port of Two Cases Am J M Sc 190 263 68 1935

[2541] Rosling E Ueb r h reditäre hemorrhagische Diathes n Acta med Scandinav 72 104 11 1929 Zbl 23 351

[2542] Rabe F and Salomon E Ueber Fas rstoffmangel im Blute bei ei em Fall v n Hämophilie Deutsches Arch f klin Med 132 240 19 0

[2543] Opitz H a d F i M Ueber eine neue Form de Pseudohämophilie Jahrb f Kinderh 94 374 1921

[2544] Macfarlan R G A Boy With No Fibrinogen Lancet 1938 1 309

[2545] Goldstein H I Hereditary Multiple Telangiectasia Goldstein s Heredofamilial Angiomatosis With Familial Hemorrhages (Rendu Osl r Weber s Disease) Arch Dermat & Syph 26 28 -309 1932

[2546] Barrock J J Hereditary Hemorrhagic Telangiectasia Wisconsin M J 43 805 858 1944

[2547] Weber F P Ha morrhagic Tela giectasia of the Osle Type Cas Brit J Dermat 48 182 193 1936

[2548] Pardo-Cast llo V an1 Fariñas E P Hereditary Multiple Teleangiectasia Arch Dermat & Syph 39 1025-1034 1939

hemorrhages Death either during the attack of untractable epistaxis or by severe secondary anemia caused by the repeated attacks has often been reported but cases without the dangerous hemorrhagic tendency are known [2549] Heredity is the third characteristic of the syndrome Unlike hemophilia the condition is not sexbound and it is transmitted by both sexes following a dominant pattern of heredity

Besides changes caused by secondary anemia the *blood* findings are normal especially with regard to bleeding and coagulation time The affected capillaries have lost their contractility on injury [2541] Splenomegaly and swelling of the liver occur frequently [2549, 2552] Scherer [2553] observed cirrhosis of the liver in both mother and daughter with Osler s disease This is interesting in view of the vascular spiders which are common in hepatic cirrhosis

Capillaroscopy reveals excessive richness of surface capillaries and lengthening or tortuosity of the loops [2545] Bommer saw aneurysms in great number but never in the retina

The histology shows the weakness or hypoplasia of the connective and elastic tissue explaining the bulging and vulnerability of the small vessels The condition must be considered as a systemic hereditary disorder of the entire connective tissue system [2554]

The therapy is mainly limited to the destruction of the individual lesion by cautery This operation reportedly often fails to stop the bleeding Houser [2555] and Fitz Hugh [2552] advise against blood transfusion if spleen and liver are enlarged

In several patients with Osler s disease some of the telangiectases of the mucous membranes were seen to diminish or disappear entirely on treatment with moccasin venom [2550]

Thrombocytopenic Purpura

Thrombocytopenic purpura is also known as morbus maculosus haemorrhagicus or Werlhof s purpura Its main feature is abnormal bleeding which may occur in any organ the skin almost never being spared All mucous membranes especially those of the nose the mouth the lungs the genitourinary and the digestive tracts may ooze blood in varying degrees of severity Cerebral and adrenal hemorrhages occur The onset is often sudden without any premonitory symptoms The course may be hyperacute acute chronic or intermittent The disease may terminate in complete restitution or in death from hemorrhage or from aplastic anemia caused by the repeated attacks No

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[2549] Milbradt W E folgr i h L i rth rapi bei ein m Fall von Tele ngiectasia haemorrhagica H re lita ia (O l r s Di ease) mit Lebe störung Arch f D rmat u Syph **166** 34-40 193

[2550] Milbradt W Atypisch diffuse Sklerod rmie mit Osl rsch m Syndrom und Leberstörung Dermat Wch schr **99** 973 979 1934

[2551] Ro enthal Oslersche Krankheit Zbl **40** 720 193

[2552] Fitz Hugh T Jr Splenomegaly and Hepatic Enlargement in H reditary Hemo rhagic Telangiectasia Am J M Sc **181** 61 268 1931

[2553] van Bogaert L and Scherer H J Hémangiomato familiale de Rendu Osl r et ci rho e hépatiqu Ann de méd **38** 290-300 1935

[2554] Ro e thal F and Unna P U ber das Wesen der Oslerschen Krankheit Klin Wchn ch **12** 865-868 1933

[2555] Houser K M He ditary H morrhagic Telangiectasia Ann Otol Rhin & La yng **43** 731 738 1934

age is immune but children and adolescents especially girls in puberty are more likely to become afflicted and their cases are more often acute The typical blood findings are low platelet count and increased bleeding time up to ninety minutes The coagulation time is normal or only moderately increased but the clot does not retract The coagulated blood remains in a jelly like condition The tourniquet test is positive Anemia and abnormalities of the leukocytic picture are absent [6] The spleen is often enlarged and tender

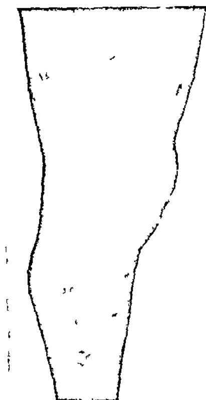


Fig 331 — Thrombocytopenic purpura Allergy to [illegible] (Courtesy Dr Erich Urbach)

Thrombocytopenic purpura is either an entity of its own the cause of which is unknown or it is caused by a known factor such as infection blood dyscrasia poisoning or liver disease E Frank called the idiopathic type essential thrombopenia (thrombocytopenia) to separate it from similar hemorrhagic diseases secondary to other conditions There is no dermatological difference between these two groups Essential thrombocytopenia is a rare disease Only about 179 cases were counted in 275 000 admissions in two American and one European hospitals These figures probably include some secondary cases The belief is gaining ground that only the shortcomings of the present diagnostic means create what is known as essential thrombopenic purpura

[6] Rosenthal [illegible] Course and Treatment of Thrombopenic Purpura J A M A 112 101 106 (Jan 14) 1939

Dermadromes —The cutaneous purpura appears in crops of varying abundance and on slight local trauma A ready tendency to bruise particularly over the shins and knees is often the first intimation of the disease [890] The purpuric spots frequently appear first on the legs and they may be restricted to the legs in less severe cases More often the crops gradually cover the whole body Petechiae and suffusions are usually seen simultaneously The mixture of both types of hemorrhagic lesions in the same patient is considered a characteristic feature of the morbus Werlhof [131] but this should not be taken too literally Some cases at least at certain times show only mucosal lesions The fresh suffusions are not always purely hemorrhagic When they appear they some



Fig 332 — Acute purpura with thrombocytopenia

times have an *urticarial* character being pink and elevated and show their hemorrhagic nature more clearly only later Such cases which are on the border line of the anaphylactoid form of purpura are rare They may be associated with edema of the ankles Suffusions can easily be produced by gentle flicking bumping or pinching They sometimes appear on areas which are exposed to pressure e g the buttocks or the shoulders The petechiae can be provoked by increased venous pressure by coughing pressing during a bowel movement etc They appear as deep purple sharply outlined pin point or lentil sized spots sometimes lined up in streaks from scratches

Change from the horizontal to the upright position may produce purpuric lesions This phenomenon known as orthostatic purpura is often marked in patients who are just recovering from an attack of thrombopenic purpura It can be observed in other types of purpura too

Purple or black spots or suggilations especially of the gums and of the oral or pharyngeal mucosa are quite common [557] This diapedetic bleeding from the mucous membranes may create a very serious condition

Pathogenesis —Thrombopenia and abnormal bleeding are the outstanding signs of Werlhof s disease Since the blood platelets are born in the bone marrow and die in the reticulo endothelial system especially the spleen their population in the blood can be influenced from both ends Depression of the bone marrow by bacterial and other poisons by radiant energy carcinomatosis and other local processes may thus result in the same thrombopenic and purpuric effects as hyper activity of the spleen The spleen may be thought of as devouring the platelets or as exerting a depressing influence on the megakaryocytes in the bone marrow possibly by means of a hormonal mechanism (For discussion of the experi mental evidence see Quick[890]) It has long been observed that however striking the thrombopenia in Werlhof s purpura may be no definite parallel between plate let count and purpura exists Sometimes bleeding occurred in moderate throm bopenia and in some cases purpura did not appear with very low platelet num bers [558] or the platelet count decreased only after the hemorrhage [2461] Mac farlane[25 3] showed in capillaroscopic photographs that the injured capillaries did not retract in thrombopenic purpura These and many other observations show that the vascular reaction more precisely the lack of vasoconstriction after injury is an important factor Quick[890] tried to connect the platelet and the vascular theories The capillary dilation is caused by histamine and one of the functions of the platelets is to remove this agent which is formed in excess In carrying out this task the platelets are rendered more susceptible to agglutina tion and lysis This hypothesis which is based on considerable evidence would explain vasodilation as well as loss of platelets The spleen or the reticulo endothelial system is possibly a major source of the histamine which kills off the platelets The opinion that allergy plays a part in thrombopenic purpura is gaining favor and is expressed in the tendency to remove the borderline between thrombopenic and nonthrombopenic purpura The main reasons for an allergic theory of thrombopenic purpura are based on the great number of cases which have been observed after prolonged and repeated medication with arsphenamine gold [559] edormid [2 60] quinine nirvanol and after ingestion of cow s milk [561] and other foods Infections for example pertussis have caused thrombopenic purpura so have blood transfusions [56] [564]

[2461]Watson Williams E Th Fau ial Lesions of Purpu a J La ynr & Otol 53 181 186 1938

[558]Roskam J Purpuras hémorragiques et thrombopénie (Etude e pé imental) Pathogénie du syn frome hémorr ique eng ndré par l administration de sérum antiplaquettes Sang 8 129 169 1934 Zbl 48 400

[559]Hu lson E H Pu pura Ha m rrh gica Caused by Gold and Ar eni al Compoun l Two Ca es Lancet 2 74 77 1935

[60]Hal H H Pu pura From Sedormid J A M A 113 674-675 1939

[561]La d berg r M Purpura nach Kuhmilch Ztschr f Kind rh 39 569 19 5

[562]Brinnitzer H N Mo bus Werlhoff mit all rgisch r Reaktion auf mütterliches Blut d r gl ich n Bl tgruppe Zt chr f Ki derh 51 566-578 1931

[564] qui r T D and Madison F W Purpura and Food All rgy J A M A 106 402 1936

[2464]Pat k A J Jr Thrombopenic Purpu a and Other Hemorrhagic Diseases Am J M Sc 191 7 3 1936

No matter what the final conception of the pathogenesis of hemorrhagic purpura will be the importance of the capillary factor is established

Treatment —The most important step toward successful treatment is to find out whether there exists a causal infection poisoning blood dyscrasia or malignant disease which may be treated In the remaining idiopathic or essential cases the tendency to remissions and spontaneous healing make an evaluation of any therapeutic procedure in thrombopenic purpura difficult However, since Kaznelson[564] in 1916 based on E Frank's work first advocated splenectomy the number of successful operations has become so large that the method is now generally considered the only means that can be relied upon when all other therapy fails[890] Many large series have been reported so that the error from spontaneous healing[566] is now small The postoperative mortality is even per cent[567, 568] to ten per cent[569] in chronic cases In Pemberton's series of fifty seven operations (Mayo Clinic) sixty three per cent were permanently cured and almost all the others improved Pemberton[568] feels that splenectomy is indicated in the moderately severe cases with a definitely established diagnosis Early and mild cases do not need splenectomy They can be treated with blood transfusions and small doses of x ray to the spleen However splenectomy if indicated should not be delayed too long[568] because the operative danger increases as the condition of the patient becomes weaker Most authors advise against splenectomy in acute cases Kosdoba[569] in a review of 168 cases estimates the postoperative mortality in acute cases to be as high as 20 to 30 per cent and in juvenile patients of the acute group 35 to 50 per cent Three out of four patients with acute thrombopenic purpura who had splenectomy died but four other patients of the same category who were treated with blood transfusions only died too[571] The postoperative mortality has come down to 13 per cent in the acute cases (Brown and Elliott after Quick[890]) but splenectomy in children must still be considered as very dangerous Smears from extirpated spleens usually do not show pathologic changes Only occasionally are the splenic blood platelets increased[6]

X ray treatment of the spleen has a hemostatic effect in many types of hemorrhagic disease Considering the relatively high mortality of splenectomy especially in juvenile and acute cases this method deserves a trial In a review of 45 cases treated with x ray Vaughan[571] found 25 cures and 20 failures About 25 per cent of the cases were acute ones which were almost all listed as cured

[564] I az el I V rs h r l r I r häm r hagi h r Diathe l el ein m l alle vo r ss ntieller Thromb op (Fra k na h Mil tirpatio j l r ok th omb olytis he Purpura Wien klin Wch s h 29 14 1 1 16

[566] Jor H W a l T a r r s I Tl T eatme t f Purpu a H m rrh agica J A M A 100 83 88 1933

[567] Elliaso I ar l F rgaso I I pl ectomy i Purpura H m rhagi a Ann urg 96 801 8 9 1 33

[568] Pemb rtor J l J Tl Di g o is a d T eatme t of Purpura H mor hagi a Am J Surg 24 93 806 1934

[569] I osdol a A S Zur B l ar liu g le es enti ll r Th ombop ni Arch f klin Chi 166 794 806 13 1

[570] Marzullo F R Tr atm nt of Purpura H morrhagi a R port of Cas s Am J Surg 22 9 9 1933

[571] Vaughan J M Treatm t of Thrombocytopenic Purpura Brit M J 2 84 845 193

Other reports are inconclusive because of small numbers or not comparable because of great differences in technique

Rudisill [572] and also Mettier and Stone [573] believe that roentgen-radiation is valuable (8 cases) in thrombopenia Doses at 200 r per sitting applied to the spleen with low intensity and heavy filtration are recommended About six treatments may be given with three days interval The platelet count has been seen to rise after the first treatment Most of the chronic cases are now operated upon the cases with poorer prognosis being left to other methods [571, 574, 577] X ray therapy is less reliable than splenectomy but practically without danger It may well tide a patient over a critical phase

Blood transfusions are of great but only palliative value Rosenthal[2, 6] sees no value in repeated small transfusions Vitamins C and B parathyroid extracts and Stryphnon [578] have been advocated Mocassin snake venom [579] is of some palliative value in chronic cases [58]

Schonlein Henoch s Non-thrombocytopenic or Anaphylactoid Purpura

After separating the thrombocytopenic purpura a group of purpuras remain which—though not without exceptions [161] has normal platelet count normal bleeding and coagulation times and normal clot retraction Usually the tourniquet test is positive [580] Allergy and infection have been increasingly found to be significant in their pathogenesis The combination with other symptoms which are well established allergic phenomena like urticaria angioneurotic edema and swelling of the joints is reflected in the term anaphylactoid [2581] Today the group would probably be called allergic purpura However there are many cases in which no allergic or infectious cause can be detected

In *Schonlein s purpura* as the anaphylactoid purpura has been and still is called the urticarial component is a characteristic feature Glanzmann[2, 81] used the term purpura urticaria for raised white or pink small or large wheals The petechiae often develop within the urticarial and slightly inflammatory lesions While the urticarial element quickly disappears the hemorrhagic part stays and undergoes the well known changes

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[572] Rudisill H Jr s essful T atment f E ntial Th ombopenia With Hemorrhage by Roentg n Ray J A M A 107 119 120 1936

[573] Mettier S R and Stor R S Effect of R ntgen Ray Irradiation on Platelet Production in Essential Thrombocytop nia Am J M Sc 191 794 807 1936

[574] Hippe H and Lochmann R Di B handlu g d r thr mbopeni ch n Purpura im I indesalter mit Rö tge bestrahlu g de Milz Jahrb f Kinderh 126 30? 309 193?

[575] Wi t ob M M Ha aha E M J and Thomas C R Purpura Haemor hagica With Special Ref renc to Cours a d T atm nt J A M A 109 11 0-1176 1937

[576] Bistolfi S La ro ntg nterapia n ll malatti a si drom morragi o Radiol med 19 773 8 0 880-933 193

[577] Birk W l ebe di A z ig n ur Rö tg b handlu g b i kind rkrankh it n und über die Fr? lg d rs ll H u III Mü he med Wchnschr 1931 II 1?19 1 ?

[578] Klina R N B ha dlu g o thrombopenisch r I u pur l lin W hnschr 1936 I 935-937

[579] Peck S M d Ros thal W Effect of Mocassin Sn k V nom (Ancistrodo piscivorus) in Hemorrhagi C o ditio J A M A 104 1066 193

[580] Gol ist in F Schö l in H noch s Purpu a R port of a Ca With R view of the Literature Clin North Am rica 12 869-881 19 8

[581] Glan mann E l urpura Fult inans Schw iz med Wchnschr 67 8?9 830 1937

Erythema nodosum and erythema multiforme like eruptions have been observed The pleomorphic character of the lesions is supposed to be an outstanding feature [8, 2580] The lesions appear in crops predominantly over the lower legs Less frequently the other parts of the body are involved The face the bends of the large joints and the palms and soles usually remain free [2131] The crops follow each other in intervals of days or weeks Recurrences have been observed years after apparent healing

The spring of the year seems to favor the first outbreak as well as recurrences The term purpura (peliosis) rheumatica refers to the combination of purpura with painful mostly serous exudations into the joints They have nothing to do with rheumatic fever

Henoch s purpura is an anaphylactoid purpura with acute hemorrhagic intestinal symptoms Heartburn epigastric discomfort abdominal colic nausea and vomiting melena constipation or more often diarrhea with bloody stools and other symptoms of acute abdominal disease are usually present and have not infrequently led to a diagnosis of appendicitis or intussusception with subsequent laparotomy [258] Purpuric skin lesions in acute abdominal conditions especially in children should make the possibility of Henoch s purpura enter the physician s mind There are showers of petechiae on the skin[976] and polymorphous skin lesions similar to those in Schonlein s purpura to which Henoch s purpura is related Unfortunately the purpura often follows the abdominal symptoms by several days which complicates the matter and explains the diagnostic errors

The allergic character of many cases of Schonlein s and Henoch s purpura has been demonstrated [258] Improvement after elimination of wheat [2583] eggs and wheat[2584] and a number of other items like pork milk potatoes chicken etc [85, 586] has been observed Allergic diseases in the family hay fever infantile eczema and preceding allergic diseases are more common than one would expect [58] The relationship to urticaria angioneurotic edema joint swellings and the resemblance to serum sickness has often been emphasized Accompanying infection is just as common Tuberculosis tonsillitis [587] scarlet fever [2 88] prostatitis (O Leary in discussion of Caro and Zeisler [589]) malaria tropica [590] may be mentioned as a few examples

Purpura fulminans is a rare fatal hemorrhagic disease which occurs in severe mostly septic infections The patients are almost always children While infections with pneumococci as well as scarlet fever and measles have occa

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[582]Alp r t in B B Alle gic I u pura an l Acute Ab lominal Symptons M Rec **154** 18 2 2 1941

[2 83]Kahn I S Henoch Purpu a Du to Fo l Allergy J Lab & Clin Med **14** 835 836 19 9

[584]Ba th lm F L Allergic Purpura J Allergy **1** 170 171 1930

[85] Alexander H L and Ey man C H Allergi Pu pura J A M M **92** 209 2094 19 9

[2586]Eye man C H Henoch s Purpu a South M J **28** 341 1935

[587]Coke H Two Inte esting Cas s of Pu pu a B it M J 3664 535 537 1931

[2 88]Pratt T A and F w H W O Purpura Fulminan Following a Mild case of Scarlet Fe r Brit M J 3560 595 596 19?9

[25] Caro M R and Zeisl r E P Recurrent Ch oni Purpu a Arch D mat & Syph **24** 70 703 1931

[2590]Burhanettin Zwei Fälle von Mala ia mit Henoch Schönlein bzw We lhofsche Purpura Dirim **8** 265-267 1937 Zbl **57** 439

sionally been followed by fulminating purpura the majority of the cases were observed in the course of meningitis

The ecchymoses in purpura fulminans occupy large areas e g entire extremities and sometimes almost the whole skin These giant lesions develop very rapidly often in a few hours The involved areas are sometimes entirely black *A certain symmetry of the purpuric lesions is striking in some cases* The platelets bleeding time coagulation time clot retraction and fibrinogen were normal in Glanzmann s case The autopsy findings are mostly negative [591] This is not the case in a group of fulminating purpuras which now can well be separated and which is known as the *Waterhouse Friderichsen* syndrome [2591 592] Only abou sixty cases have become known since Marchand (according to Glanzmann [593]) in 1880 first observed a case of this kind The terminology should give credit to Little [594] who in 1901 ten years before Waterhouse and seventeen years before Friderichsen published twelve cases the greatest contribution of a single author

The syndrome occurs mostly in children younger than one year but it has been seen in adults [259] The onset is very sudden often with abdominal pain and vomiting moderate fever and flushed face The patient soon becomes stuporous this may be mistaken as healthy slumber [2596] After ten to twelve hours cyanosis which may alternate with ashen gray pallor is striking In this stage showers of petechiae may appear over the whole body The purpuric spots increase rapidly sometimes under the very eyes of the observer They may coalesce and produce a blotchy appearance On the buttocks back and extensor surfaces of the arms they may look like postmortem lividity The rash remains until death Rarely the petechiae stay small According to Aegerter [596] no skin lesions showed in thirteen out of fifty seven cases

Headache and other symptoms of the nervous system profound weakness spiking temperatures from subnormal to 108°F low blood pressure and circulatory disturbances are often mentioned Cervical rigidity is usually absent Almost all patients died within a day or two The diagnosis is rarely made ante mortem Leukocytosis is mentioned in seven cases [598] In two cases[2-81 597] the platelet counts were extremely low in two others normal Most of the other cases do not mention hematological findings [598] Coagulation and bleeding time have been found normal several times Hypoglycemia and elevation of nonprotein nitrogen of the blood has been described [598] At autopsy the out

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[591] Waterhou R A Cas of Ad nal Apopl y Lancet 1911 1 577 578

[592] Friderich n C Neb nnierenapoplexie bei kl inen Kindern Jahrb f kind rh 87 109 1 5 1918

[593] Glanzma n E Beitrag zur Klinik Hämatologie und Pathologie des Synd oms von Waterhou e-Frid richs n (Neb nierenapople ie bei klei en Kindern) Jahrb f Kinderh 129 49 63 1933

[594] Little E G Cases of Purp ra Endi g Fatally Associated With Hemorrhage Into Suprarenal Capsules Brit J Dermat 13 445-467 1901

[595] Thomas H B a l Leiphart C D S pticemia and Purpura With Adrenal Hemorrhage in th Adult J A M A 125 884 890 1944

[596] A ge ter E F Th Waterhouse-Fri leri hs n Syndrome A Review of th Lit rature and a R port of Two Cases J A M A 106 1715 1 19 1936

[597] Le inson S A W t rhouse-Friderichsen Syndrom Case With Autopsy Findi g J Pediat 14 500-516 1939

[598] L sher S J Wat hou e-Fri le ichs n Syndrome Canad M A J 38 232 1939

standing finding in 95 per cent of the cases was destructive bilateral adrenal hemorrhage Often no adrenal tissue could be made out

It is now certain that most of these cases are caused by meningococcic infection probably with a massive invasion of meningococci into the blood stream Just as in other rashes of meningococcic disease meningococci have been found in the purpuric lesions [599, 600]

Purpura annularis telangiectodes Majocchi and Schamberg s disease two related purpuric skin diseases have some internal relationship (See Polycythemia)

Recently E Davis [601] has given a statistical analysis of 500 consecutive cases of purpura This large series provides an idea of the frequency of the various types of purpura The diagnosis of purpura simplex was made in 15 per cent Schonlein s purpura in 2 per cent Henoch s in 0 4 per cent hereditary familial purpura simplex 15 per cent primary thrombocytopenia 0 8 per cent hemophilia 0 2 per cent and pseudohemophilia familial or nonfamilial in 1 per cent The rest (63 per cent) was grouped under the many types of symptomatic purpuras in infections poisonings etc

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[599] McLea St and Caffey J Ft l mi Purpuric Me l gococ u B ct remia l Early Lif Diagno tic Values of Smears From Purpuric Lesions Am J Dis Chil l 42 10 3 1931

[600] Latte G Su di un caso di porpora fulmi ant Pediatria (Ri) 39 3 3 381 1931

[601] Davi F Purpura of Skin 00 C s s Lancet 1943 2 160 161

CHAPTER XXXV

DERMADROMES OF INTERNAL CANCER

Internal cancer may manifest itself on the skin by *metastases* by *nonspecific dermadromes* and by *acanthosis nigricans* [60]

Cutaneous Metastases —It can generally be said that only mammary cancer in advanced stages as well as occasionally after the operation of cases on the borderline of operability reach the skin frequently by direct extension by operative implantation or by lymphatic metastases

The contiguous metastases appear as painless nodules which grow rapidly and if dense enough coalesce into large hard masses which may surround the chest wall like armor (Cancer en cuirasse) Sometimes the diffuse invasion of the skin forms an evenly red sharply and jaggedly outlined area of inflammatory cancer which is known as erysipelas carcinomatosum

Skin metastases from visceral cancers are rare probably occurring not more often than in 1 [603] to 3 per cent [2604]

Since there is no flow of lymph directed from the viscera toward the skin the metastases are likely to originate from a primary lesion or still more often from secondary cancers in the lungs [603] or in the liver This fact accentuates the *ominous significance* of all skin metastases of visceral cancer

Adenocarcinoma of the stomach occasionally produces an outcropping of hard mostly red nodes scattered in moderate numbers over the skin Firm scleroderma like plaques in the skin have also been seen [260] [2606] Dermal secondaries of hypernephromas prostatic or breast [606] cancers have been found in the scalp suggesting sebaceous cysts [667] or turban tumors [607] The upper abdomen and the umbilicus have relatively often been seen to develop metastatic growths originating from the stomach ovary or uterus They are direct subsidiaries of metastatic nodules in the liver from which they travel through the ligamentum teres [604-606]

Rectal carcinomas may develop sessile or pedunculated metastases about the buttocks [667] Only a few cases of cutaneous lesions from ovarian carcinoma have been reported [1448] Several of the cases showed firm plaques or confluent nodules in an edematous purplish brown skin which were not very suggestive of metastatic cancer The lesions resembled erysipelas or more correctly the

[2602] Rothman S L t r Hauterschei ung n bei bösa tig n Ceschwülst n inner r O gane Arch f Dermat u Syph 149 99 1 3 19?

[2603] Walth r H E M tastases of Cutaneous Carcinoma and Secondary Skin Tumors Schweiz med Wchnschr 71 995 100? 1941

[2604] Gates O Cutaneous M t tases of Malignant Diseas Am J Cancer 30 718 729 1937

[2605] B ck S C Epith liome H ndl d H u Ck 12 3 395-403 1933

[2606] Bade W Das m tastatisch Carcinom de H ut im Anschluss an Carcinom Innerer Organe Arch f Dermat u Syph 179 7 8 1939

[2607] Ronchese F Metasta es of th Scalp Simulati g Turban Tum rs Arch Dermat & Syph 41 639-645 1940



Fig 333 — Outcrop m tastases from cancer of the stomach



Fig 334 —Skin metastases from cancer of the stomach

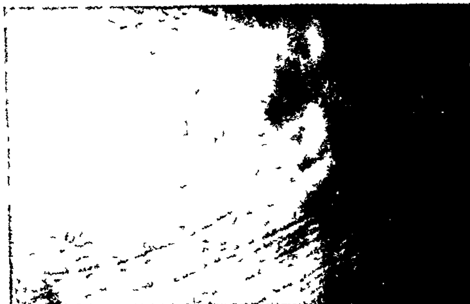


Fig 33 —Lymphosarcoma cutaneous metasta es Forehead



Fig 335 —Skin metastases from lymphosarcoma

erysipelas carcinomatosum of the breast The biopsy however revealed metastatic ovarian carcinoma Bronchial carcinomas metastasize to the skin relatively often [603]

A rare event is the hematogenous spread of a cancer developing from the epithelial lining of an *osteomyelitic sinus* Crops of metastatic nodules have appeared in the skin of the upper arm after the amputation of an osteomyelitic finger [608]



Fig 337 —Cor g te l vel l car i o a of the ophag

Lymphosarcoma and melanosarcoma are probably more apt to metastasize to the skin than the other more common cancers They both form cutaneous and subcutaneous nodules or plaques which in some cases appear on the surface in enormous numbers The metastases of melanoma are in one out of three cases entirely or partially pigment free (amelanotic) the melanotic character of the cells being demonstrable only by the positive dopa reaction [603]

[608] Stewart C D Obermayer M E and Woolhandler H Cutaneous Metastatic Carcinoma Originating From Osteomyelitic Cavities Arch Dermat & Syph 41 545 50 1940

Conclusions with regard to the *site of a primary* tumor from the distribution or clinical appearance of skin metastases are less reliable than the pathologic picture

The skin does not seem to offer a good soil for the cancerous seeds Skin nodules have been seen to disappear *spontaneously* [609, 610] and they usually appear quite *radiosensitive* this can be interpreted as a lack of vitality A few hundred roentgen units may make them disappear but of course there is no more than palliative benefit for the patient from treating metastases However it is not true that cutaneous metastases indicate a particularly fast rate of growth of the primary tumor or that they herald approaching death The patients may still live many months or even years [604-611] Three years of life have been recorded in a case of adamantinoma of the mandible after distant metastases had appeared on the temple [604] Three to six months is the average time a patient will live after the appearance of skin metastases

Nonspecific Exanthems —A still rarer dermadrome of internal cancer is the *nonspecific exanthem* These eruptions range from simple pruritus and prurigo like eruptions with hyperpigmentation to bullous multiform and eczematoid rashes Typical dermatitis herpetiformis [60] lupus erythematosus acutus pellagroid and exfoliative dermatitis [61] generalized urticaria [613] purpura [2614] and purpuric dermatitis with widespread superficial necrosis are on record [260, 61] Thrombocytopenic purpura [616] may be caused by massive invasion of the bone marrow by metastases In some cases [617] a generalized polymorphous exanthem was seen in x ray treated malignancies of the mouth and neck Drug eruptions from barbiturates are difficult to rule out in some of these instances

The rashes especially pruritus may precede subjective or objective signs of cancer and they may disappear after successful removal of the neoplasms [261] The peculiar tendency to multiple peripheral thromboses and short clotting time in pancreatic cancer have been mentioned (see pancreas) The exanthems in internal cancers are interpreted as reactions to metastasized tumor cells which have been destroyed by cutaneous defense mechanisms [615]

Diffuse deep *bluish black discoloration* of the face neck and hands together with melanuria in a case of widespread metastases of a malignant melanoma was

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[609] Sézary A Horowitz A and Mig t A Epithéliomas m ta tasiques de la p au Bull So f a ç d dermat et yph 40 1 91 1?34 1933

[610] Du Bois Ca c r d la la gu t mét tas s cutané Schweiz med Wchnschr 1928 II 1051 1059

[611] Kaufman Wolf M II utm tastas n im A hl ss harzinom in e er O gane Arch f Dermat u Syph 114 709-744 1913

[612] Schw igl R Frythrode ml u I t t ru karcinom Zbl f Gynäk 57 94 99 1933

[2613] Urbach F En loge ou All rgy Arch Dermat & Syph 45 697 722 1942

[261] Stillma R G Col idenc of M lign nt Tumor and Purpura Hemorrhagica M Clin North America 14 1533 1538 1931

[615] Becker S W Kahn D and Rothman S Cuta eous Manifestations of Internal Malignant Tumors Arch De mat & Syph 45 1069 1080 194

[616] Blum I U be symptomatisch Thrombope i b i Magen arcinom Med Klin 24 1200 1 0? 1928

[617] Lowe L and (aml I M R F anth m Complicati g Neopla tic Dis ase 4 Cases Am J Roentg nol 43 587 596 1940

seen by Odel Montgomery and Horton[2618] The authors assumed involvement of the adrenal glands and chromaffin tissue

The eruptive appearance of senile *hemangiomas* (ruby points) in relatively young persons has been *disproved* to be suggestive of visceral cancer[1580] Schridde[619] claimed that the occurrence of dark pigmented coarser hairs of dull surface especially on the temples but also in the eyebrows and beard were indicative of cancer They were even found among blond and gray but not among red hairs This claim still lacks confirmation



Fig 338 —Acanthosis nigricans (Courtesy Dr M Jessner)

Acanthosis nigricans is a dermatosis of remarkably uniform appearance The disease is rare about 400 cases have been recorded since S Pollitzer[2620] in collaboration with P G Unna published the first case in 1890 (see also Pollitzer[2621]) The significant elements of the gross skin changes are a characteristic *distribution papillary hypertrophy hyperpigmentation and hyperkeratosis* The sites of predilection are the axillae the nape of the neck the genitals the inner

2618 Odel H M Montgomery H and Horton B T Diffuse Melanosis Secondary to Malignant Melanoma Proc Staff Meet Mayo Clin 12 742 747 1937

2619 Schridde H Krebshaare Münch med Wchnschr 69 1565 1566 19

2620 Pollitzer S Internat Atlas selt Hautkr 10 1890

2621 Pollitzer S Acanthosis Nigricans J A M A 53 1369 1373 1909

thighs the elbow bends, the umbilicus the perianal region and the dorsa of the hands and feet In some cases the lips the anterior neck the areolae of the nipples and large areas of the trunk may also be affected There is almost in all cases marked symmetry provided the picture is fully developed

The affected skin is densely covered with mostly smaller than pea size sessile nodules with a more or less rounded top Many of them especially in the axillae and on the nape are crowded into rows or small groups and separated by the natural furrows of the skin Among the great number of little papules is scattered a much smaller number of larger ones forming a picture comparable to the fungi form papillae among the filiform papillae of the tongue In the folds cauliflower or cock s comb resembling growths have been observed

The color of the lesions varies from gray slate or yellow to all shades of brown and black The melanosis often extends beyond the papillomatous area Some times gross hyperpigmentation is missing the lesions then having a yellow orange hue *Depigmentations within the darkened areas are due to inflammation* Scattered nevus like hyperpigmented lesions in apparently unaffected skin are frequent concomitant efflorescences which may appear in great numbers [6 2] Scaling dryness or palpable roughness as gross expressions of hyperkeratosis are present but are not prominent features The palms and soles are often hyper keratotic [26 3] but they remain free of hyperpigmentation Pruritus is sometimes present

The disease starts gradually most often under the arms and progresses slowly The pigmentation is increased by exposure to light the papillary hyper plasia by friction and maceration

The oral *mucosa* and the transitional skin of the lips and of the vulva par ticipate in the papillary hyperplasia in about one half of the cases The dorsum of the tongue may take on a furrowed appearance resembling lingua plicata and the papillae may be enlarged and rough like those of a cat s tongue Even thin spines have been described [6] Similar papillary or granulated surfaces may be seen on the palate the line along the bite on the buccal mucosa the epiglottis and even in the larynx Mucosal pigmentation is rare but it has been observed often enough to discredit its absence as being a distinguishing characteristic against Addison s disease and other melanoses The esophagus [6 4] the rectum and the lower part of the vagina often participate in the process

The *hair* is usually destroyed in the affected areas

The *nail* beds may be pigmented and the nails longitudinally grooved

The *histopathology* reveals enlarged and elongated papillae hyperpigmenta tion in the basal cell layer acanthosis and hyperkeratosis A small amount of inflammation is present Hypertrophy of the sebaceous glands has been noted [6]

It is customary to distinguish between a *benign* and a *malignant* type of acanthosis nigricans There is no difference in the morphology of the two types

[1571] Moncorps C Keratosen Acanthosis nig icans in Handb d H u Gk 8 37 -40 1931

[262] Küttner H Die Akanthosis nigricans und ihre Bedeutung für die Diagnose d s malignen Tumors Mitt a d Grenzget d Med u Chir 39 276-296 19 6

[6 3] Tesseraux H Über Acanthosis nigricans bes über einen Fall mit Beteiligung der Speis röhre Virchows Arch f path Anat 279 253 261 1931

[263] Yamada K A Case of A anthosis Nig icans Jap J D rmat & Urol 25 61 19 5 Zbl 19 744

The adjective malignant refers to the association with malignancy not to a malignant course of the dermatosis itself The benign type is also often called juvenile because many cases start in early childhood and remain stationary throughout later life Some of these patients died later of cancer Some of the juvenile cases were malignant and some adult cases at least clinically were not associated with malignancy [6 6] Thus there is no sharp borderline between the two types The etiology and pathogenesis of acanthosis nigricans is far from being understood but there are some facts known which eventually may lead not only to the elucidation of the remarkable phenomena of this disease but also of other pigmentary disorders



Fig 339 —A tho i nigri ans Ob sity Juve il ca no malignan y (Courte y Division of D r matology D partment of M i cine University of Chi ago)

The most important etiologic fact is that at least 50 per cent of the cases of *acanthosis nigricans occur in patients with cancer* Fully 92 *per cent* of these malignancies were found in the *abdominal* viscera mostly in the stomach Almost all of the nonabdominal cancers had abdominal metastases [2627] The course of many neoplasms associated with acanthosis nigricans is highly malignant

[2626]Burgess N A Cas of Acantho is Nigri an Brit J Derm t 43 169 177 1931

[2627]Ollendorff Curth H Ca er As ociated With A antho i Nigri s Ca Arch Su g 47 517 552 1943

In trying to explain the peculiar pigmentary skin disease which has some features of Addison's disease the thought of an adrenal etiology has arisen. However, at least twelve cases are on record in which autopsy failed to show any adrenal involvement. H. O. Curth[26,7] who has recently reviewed the available material with regard to other endocrine glands arrives at the conclusion that "theoretic considerations and actual records of cases speak against endocrine

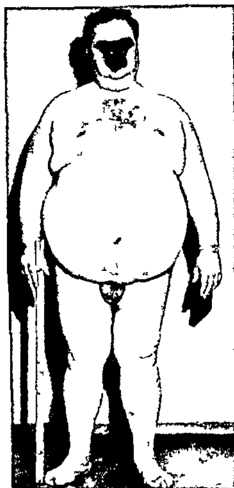


Fig 340 —Obesity of pituitary type in a patient with acanthosis nigricans (Courtesy Division of tology Department of Medicine University of Chicago)

disturbances as a causative factor in acanthosis nigricans." Yet a great number and variety of endocrine disorders have been found in association with acanthosis nigricans. It seems that although at the present time no satisfactory endocrinological etiology can be propounded the described associations with obesity, debility, dwarfism, genital hypoplasia, diabetes, goiter, cryptorchism, achondro

plasia and acromegaly cannot be slighted Puberty exerts a provoking influence on the onset or development [2627] Of great interest is the case of Hellerstrom[2626] who observed marked though not complete regression of the diffuse papillomas after castration of a male patient Ketosteroid determinations do not seem to have been done in acanthosis nigricans In a few cases the dermatosis subsided after treatment of the cancer and recurred with it (Spieschka after Moncorps [62]) Spreading of acanthosis nigricans after stationary periods seems to coincide with the development of cancer [2627] These observations point to the neoplasm itself as a cause But the great rarity of acanthosis nigricans compared with the frequency of abdominal neoplasms compels one to believe that a rare combination of factors must be required The same conclusion must be applied to the association with other diseases The dermatosis usually preceded in some cases for many years the development or at least the discovery of cancer The etiologic role of the abdominal *sympathetic* system is not yet clear Stimulation of the chromaffin system could explain the hyperpigmentation but not the other aspects of the syndrome Most cases have not been investigated thoroughly from this view point In one case the resection of a cervical ganglion resulted in rapid regression of acanthosis nigricans in the axillary areas [672] Ten instances of *familial* occurrence all of the benign type have been observed [6 7]

The *treatment* of acanthosis nigricans is at best symptomatic unless regression occurs after extirpation of the malignancy The *prognosis* of juvenile acanthosis nigricans as a dermatosis is that of an incurable though in itself not dangerous anomaly comparable to a widespread nevus However the prognosis of the juvenile benign variety is darkened by the frequent association with systemic disease The *prognosis* of the cases starting in the age group from 20 to 40 years is doubtful Acanthosis nigricans which develops after the age of 40 is almost certain to be indicative of cancer usually visceral [6 9] which when the dermadrome appears already has metastasized Exploratory laparotomy is inadvisable (O Leary in discussion to Michelson [354])

[2626] Hellerström S Zur Kenntnis der Acanthosis nigricans Acta dermat -venereol 14 86 98 1933 Zbl 46 189 1934

[2627] Mason J C and Montgomery H Acanthosis Nigricans and Pelvic Malignancy Proc Staff Meet Mayo Clin 11 113 117 1936

Chapter XXXVI

DISORDERS OF THE NERVOUS SYSTEM

The function of the skin as an organ of sense may become affected by disturbances of the peripheral sensory nerves as well as of the central nervous system Cutaneous secretion pilomotion vascular tonus and trophic balance depend on the autonomic nervous system the functioning of which may be disturbed by local organic lesions as well as by reflexes and hormonal activations originating somewhere else These considerations give us an idea of the complex mechanisms by which a great variety of noxae including malformations injuries infections poisonings and endocrine disorders may produce dermadromes of neurogenic character

Cutaneous Senses [1339, 2630, 2631]

A variety of specialized nerve endings gives the skin the character of a sense organ The perception of all cutaneous stimuli is not diffuse as it seems to be but localized in points which are distributed over the skin in varying density The end organs related to the sensitive spots are highly specialized in their functions Thus forcing of a needle into a Meissnerian body does not cause pain but only the sensation of touch The *warmth* spots are most dense on the face and on the lateral aspects of the fingers (2 per square centimeter) The *cold* spots are much more numerous with the greatest density on the face and on the trunk About 11 cold spots can be mapped out on one square centimeter of facial skin [2631] About one third of the body surface is unable to perceive warmth

Free nerve endings in the epithelium radiating from subepithelial plexuses receive the stimuli causing the sensation of *pain* The skin has only one quality of pain but differences in intensity and duration may cause such varieties as burning pricking and soreness Lewis and Hess [63] believe that pain is caused by a substance produced in the tissue and acting on the endings of the pain nerves This hypothetical substance does not seem to be histamine

The pain spots are most dense in the popliteal fossa with 232 per square centimeter and least dense on the tip of the nose with only 44 per square cm [2631] The sense of *touch* is also localized in points which are mostly situated at the hair follicles The nerve endings surround the follicles like a basket The bent hair acts as a lever and intensifies the pressure on the end-organs The hairs widen the perceptive area of the follicle and make the point system appear diffuse A shaved area is considerably less sensitive to touch than a hairy one [1339] The

[2630] Guttmann E Haut u d Nerven-System Ha db d H u Gk 4 2 1 1301 1933
[2631] Von Frey M and Rein H Physiologie d r Haut Han lb d H u Gk 1 2 19 9
[63] Lewis T and Hess W Pain Derived From the Skin Mechanism of Production Heart 1 39-61 1933

sensation caused by a constant stimulus, for example the bending of a hair, soon fades and is no longer perceived. This phenomenon is called adaptation. Because of adaptation we do not feel the weight of our clothes, and a needle prick is painful only for a moment. The pain will stop in spite of the fact that the needle is still sticking in the skin. We do not feel a temperature which does not change.

Nerve Section—The effect of cutaneous nerve section was studied in famous self experiments by Head. Foerster [633] in evaluating nerve injuries caused by gun shots during and after the first World War, and other authors [634] modified Head's observations to some extent.[630] The section of a sensory nerve immediately abolishes all forms of skin sensibility. The areas of thermal, tactile and analgetic anesthesia after section of the nerve are not entirely congruous. Section of the ulnar nerve for instance leaves a zone, in part two inches in width, in which only pain, but not touch or temperature, can be felt. The disturbance of the perception of temperature is more extensive than that of touch and pain, and the loss of the perception of warmth is more extensive than that of cold.[631] *With the regeneration of the nerve the sensibility returns in two stages.* The two stages are explained by some authors by the existence and the difference in the regeneration of two kinds of fibers.[63] After seven to thirty weeks a markedly punctate sensibility appears with relatively wide anesthetic areas in between. However, the perception of intensities and the localization of a punctate stimulus is inaccurate and radiating widely from the point of stimulation. The threshold for pain is high, and the character of the pain is described as "sickly," meaning of an unusual quality. This quality is illustrated by the peculiar sensibility of the cornea and the glans penis which normally are of similar character. The author can, from his own experience with a severed lingual nerve, confirm the statement of Trotter and Davis (after O. Foerster [633]) that the character of the pain is different *from the normal sensation of pain. Only extremes of temperature are recognized in this stage.* The temperatures between 24 and 38°C do not cause a sensation of heat. This first stage of the return of the sensibility is called protopathic sensibility.[636] It is followed by the return of the sensation of light touch, of tactile localization and discrimination, as measured by the ability to recognize two compass tips as two distinct points, and finally by the restoration of normal sensibility. The second stage of recovery is referred to as epicritic sensibility. Complete restoration of the sensory functions may take up to two years. In skin grafts the sensibility returns after 1 to 12 months and progresses centripetally.

The section of a nerve abolishes the sensory functions in only part of the innervated area. Overlapping of neighboring innervations creates marginal hypoesthetic zones. *A persistent circumscribed dermatitis may occasionally follow* the section or injury of a nerve. These lesions are restricted to the area supplied.[637] They have been used as evidence for a neurogenic theory of eczema

[633] Foerster, O.: Symptomatologie der Schussverletzungen der peripheren Nerven, Berlin, 1929, Julius Springer.
[634] Lanier, L. H., Carney, H. M., and Wilson, W. D.: Cutaneous Innervation, Arch. Neurol. 34: 1-60, 1935.
[635] Rothman, St.: Physiology of Itching, Physiol. Rev. 21: 357-381, 1941.
[636] Head, H.: Sensibilitatsstorungen, Berlin, 1898.
[637] Herrick, R.: Dermatitis Following Nerve Injury, Arch. Dermat. & Syph. 26: 879-881, 1932.

The sensibility of the skin is considerably influenced by the vegetative system For example partial nerve section alone rarely causes circumscribed pruritus or hyperesthesia This could however be experimentally produced by simultaneous nerve section and sympathectomy [638] Vitiligo and canities have often been observed in the area supplied by peripherally diseased nerves frequently with neuralgia [11 5] This is most often seen in neuralgia of the trigeminal nerve Zosteriform pigmentations after nerve injury are also known Paresthesias like numbness or formication give little information about the nature of the nervous lesion [630]

Nerve injury section and central destructive processes may cause *trophic ulcers* The trophic i e the nutritional balancing influence of the nervous system cannot be denied The much disputed and not definitely answered question of specific trophic fibers does not seem to be important any longer since the trophic effects can be sufficiently explained by the known functions of the vegetative system [639] Trophic ulcers are mostly seen on the pressure points of the feet and other sites subject to trauma or infection e g hands nasal septum and the mouth [640] The perforating ulcer has been observed in a great variety of organic lesions e g peripheral nerve injury or therapeutic dissection [640] postencephalitic states tabes syringomyelia cervical rib [641] and others The ulcer starts as a blister or a sinus underneath a callus Keratosis of the edge and absence of granulations in the floor are characteristics of the fully developed lesion The size and course are variable Keratosis and sinus formation may be excessive causing deep destruction of bones

Itching Superficial and Deep Tickling The dermatologically most important neurocutaneous symptom is pruritus Itching can be elicited by vibrating or constant subthreshold tactile stimulation i e tickling [2030 635 64] If the stimulus exceeds a certain threshold the normal sensation of pain or touch results and replaces the itching sensation Scratching relieves itching by replacing it with pain to which itching has many relations [635] Anesthetic areas as a rule do not itch Intact perception of touch and pain is usually [643] but not necessarily a prerequisite for the eliciting of itching by superficial tickling i e light stroking with a hair or wisp of wool Thus itching or superficial tickling may still be felt if a hair is lightly run over an analgetic zone in a tabetic when a needle prick fails to cause pain In peripheral neuritis tickle is increased where there is intensification to all forms of adequate painful stimuli In syringomyelia a loss of pain and tickle seem to coincide *With lesions in the optic thalamus*, there is often intensification of the response to tickling stimuli over the same side of the body on which the responses to painful stimuli are exaggerated With lesions of the internal capsule and cerebral *cortex* which have resulted in impairment of sensibility

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[638] Aubrun E A Action vascul l e t action du ympathique dans le prurit par én rvation sensitive parti lle Compt r nd Soc de Biol 111 491-48 1937

[639] Tomma I L Si tema neuro-en loc ino e ut Gio Ital di de mat sif 75 373-433 1934

[640] Da l J Ulcères trophiques d la bouche et des fosses nasales (mal pe forant bucconasal des tabétiques) t l probl m des u ts trophiques Ann. de D rmat 8 9 139 1937

[641] Weidman F Cervical Ribs (I skin diseases) Arch. Dermat & Syph 35 716 1937

[642] Pritchard F A B The Clini al Significance of Variations in Tickl Sensit ility Proc Roy Soc Med 26 69 704 1933

neither tickle nor pain sensibility is impaired both are occasionally overactive [51] This is explained by the assumption that the tickle sensation is conducted by the peripheral neurons to the cord where the pathways cross to the other side in the posterior commissure run through the cord and the medulla near the spino thalamic tract and are *finally registered in the optic thalamus not in the cortex* [51] Therefore cortical depressants like morphine paraldehyde and bromine do not influence itching as much as thalamic drugs like phenobarbital [543] Section of the anterolateral tract of the spinal cord abolishes tickling and itching at the corresponding level while section of the posterior tracts exaggerates these sensations and protopathic pain to which itching is intimately related [2625]

Drugs which paralyze the sympathetic system like ergotamine tartrate or stimulate the parasympathetic system like yohimbine and muscarine seem to inhibit itching Konigstein[2644] concludes from these observations that the sympathetic system plays a part in the genesis of pruritus Pruritus seems to be closely connected with dilation of the smaller vessels It is perhaps a response to changes in the state of permeability [645] The psychogenic influence is powerful This also underlines the importance of the sympathetic factors Scratching as a prompt reflex reaction to itching is not fully developed before the age of one year [646] but general reactions may be seen as early as the sixth hour of life *Deep tickling* is entirely different from superficial tickling and itching though the same word is often used indiscriminately One should speak of deep tickling when the sensation is felt in deeper structures and when a considerable pressure is necessary to elicit it Von Frey [647] relates deep tickling to the sense of pressure *superficial tickling to the sense of pain* Tickling is mainly though not exclusively confined to certain areas like the anterior aspect of the neck the armpits the abdomen and the clitoris A sensation more similar to deep tickling than to itching occurs in the mucosae too e g rectum urethra larynx and trachea A characteristic of deep tickling compared with itching is its relation to uncontrolled reflexes like laughter and other widespread muscular contractions The erogenic effect of tickling is well known [51] [648] Tickling does not elicit scratching but muscular defense

Head s hyperalgetic ones are due to the projection of visceral pain to certain segmental skin regions These regions correspond to those observed in herpes zoster Head [636] mapped such skin zones for many internal organs (see M Lewandowsky [649]) The validity of the phenomenon has been amply confirmed though there are many controversies over details It should be emphasized that

Ehr w ll H and K ig t in H J li ische und e pe im nt ll Unt rsuchu gen üb r das Ju kg fühl W klin Wchn hr **42** 133 1398 19 9 H

I i i t i H Zur F t t hu ig u id B kämpfung des Ju kreizes Wi n klin Wchnsch **1** 815 816 1936

[2644] B k W Di Bed utung d veg tati Syst m für die E it tehung des Juckens De-lil ratio i N th I t nat l o g D rmatol gy Bu lap st **1** 1 9 193 Zbl **53** 458

[2646] Hartma i I a j lu D Ju k mpfi dung I r tz n I ilomotor i fl x im Säuglingsalter Jahrb f K i d rh **132** 140 1931

[2647] Vo i Fr y M I t r I Kitz I Ztschr f Ar tl F tbild **22** 81 83 19

[2648] *Dunba H I Emoti i s n i Bodily Chang N w York 1935 Columbia University Pr ss*

[2649] Dunbar H F Phy i al a d Me tal R lation hip in Ill i ss Am J P y hiat **91** 541 56 1934

[2649] Lewa idowsky M Di ntral Sensibilitätsstöru gen Handb d Neurologie Berlin 1910 Julius Spring r

Head s zones are hyperalgesias The sensibility to touch is not increased The diagnosis of Head s zones is made by needle pricks or by slight pinching Alterations of the sensation caused by tickling with a blunt object have been found to correspond with Head s zones These zones of decreased, rarely increased sensitivity to tickling are supposed to occur more frequently than the hyperalgetic zones They indicate the same organ relationship [60] A vasomotor reaction to a weak galvanic stimulus can also be used [61]

Herpes zoster of the corresponding region may though rarely be the only manifestation of a visceral disease e g peptic ulcer gallstones or cardiac disease [65] It is assumed that the viscero cutaneous relation which consists of viscus sympathicus—intervertebral ganglion—ramus visceralis—gray matter of the spinal cord—anterior root—spinal nerve—skin is affected in the intervertebral ganglion which probably becomes the site of the herpes zoster infection An interesting visualization of the cutaneous zone corresponding to a lung focus was observed after a weak ultraviolet radiation Only the skin corresponding to the tuberculus lung focus showed an erythema [61] Circumscribed edema in the viscero cutaneous zones has also been observed [651]

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[266] Krieger H Ve änderungen des Kitzelgefühls der Haut bei Organ rkrankungen Würzburger Abhandlungen vol 26 No 6 Leip ig 1930 Curt Kabitzsch

[2651] Kahane M Die cutane Diagnost k inn rer Krankheiten Wien Arch f In Med 3 6 110 19 1

[265] Arnstein A Herpes zo t r als einziges manifestes Symptom von im übr gen latent ve laufende Erkrankungen innerer O gane Wien klin Wchnschr 34 13 14 19_1

Chapter XXXVII

DISORDERS OF THE NERVOUS SYSTEM

The Autonomic Nervous System

The autonomic or involuntary nervous system innervates the sweat glands the musculi arrectores pillorum and the tonus of the blood vessels probably also the secretion of the sebaceous glands Almost every cell of the skin is sur rounded by an extremely fine reticulum of sympathetic fibrils the so-called sympathetic basal plexus or terminal reticulum (Stöhr after F John[2653])

Sweating —The innervation of perspiration has a subcortical center in the hypothalamus From there the sudomotor impulses descend through the brain stem the medulla and a series of spinal centers to the anterior roots and the peripheral sympathetic pathways (Walker after Rothman[2654]) A major crossing *takes place in the lower pons*[2655 2656] *The pathway of the sweat inhibiting action* runs through the posterior roots[2630] In spite of their sympathetic pathway the sudomotor fibers behave like parasympathetic or cholinergic nerves Their stimulation causes liberation of acetylcholine in the skin and therefore can be suppressed by atropine and enhanced by physostigmine The formation of acetylcholin in the venous return of a perfused cat leg has been demonstrated with the eserinized leech preparation[2657]

Sympathectomy and the section of a peripheral nerve (e g the sciatic) causes anhidrosis in the area supplied and hyperhidrosis in the surrounding margin[2658 2659] A reflective hyperhidrosis can be observed in the corresponding symmetric zone[2660] Sweating tests are used in the diagnosis of postural hypo tension and in determining the degree of completeness of sympathetic denerva tion after sympathectomy and removal of sympathetic ganglions[2661]

[2653] John F Skin as Organ Controlled by V g tative Nervous System Med Welt 13 985 988 1939

[2654] Rothman S Role of Autonomic Nervous Sy tem in Skin Diseases Psycho om Med 7 90-96 1945

[2655] Peet M M and List C F Changes of Sweating in Lesions of Pons Medulla Oblongata and Uppe C rvical Cord T Am Neu ol A 61 0 95 1938

[2656] List C F a d Peet M M Sweat Secretion in Man Sweating Respon es in No mal Persons Arch Neu ol & P ychiat 39 12 8 1237 1938

[2657] Dal H H and Feldberg W Chemical Transmission of Secreto y Impulses to Sweat Gland of Cat J Physiol 82 1 1 128 1934

[2658] Frölich A and Zak E Untersuchungen über d pe iph re Schwei ecr tion Naunyn Schmiedebergs Arch 168 620-637 193

[2659] Ack rmann A Studien zur Phy iologie der Schweissdrü en Dermatologica 79 219 230 30 332 1939

[2660] Guttmann L Motorische und eg tative Grenz onenr flexe bei Laesionen pe ipherer und zentraler Abschnitte des Nervensyst ms Z Neurol 147 291 307 1933

[2661] Brown G F Clinical Tests of Function of the Autonomic Nervous Systems J A M A 106 353 357 1935

The spinal centers of perspiration and piloarrection have been mapped and tabulated by Ottfried Foerster [630] Central cerebral lesions may cause contralateral hyperhidrosis (hémiplégie sudorale Binger and Berg after Marchionini [66] [663] This however is only marked in early lesions since compensatory mechanisms soon develop and some fibers remain uncrossed Unilateral mostly facial hyperhidrosis is seen in connection with peripheral sympathetic disturbances mostly injuries of the parotid area [664] or after thyroidectomy [665] Unilateral sweating is often combined with flushing facial paralysis and disturbances of the parotid gland

Ackermann [659] found sweat secretion to be the resultant of two antagonistic processes In the proximal section of the gland sweat is secreted through parasympathetic impulses In the more distal part of the tubule a regulating resorption under parasympathetic and sympathetic influences may take place [666]

Our knowledge of the autonomic innervation of the *sebaceous glands* is meager A well known fact is the seborrhea which sometimes follows brain lesions especially of the midbrain and pons (see section on encephalitis)

The psychogalvanic reflex or the Tarchanoff Veraguth phenomenon is the decrease in the *electric resistance of the skin* caused by sensory stimuli and psychic excitement The electric resistance depends on the amount of sweat and is one of the most sensitive psychosomatic reactions Any psychic concentration emotion or effort measurably increases the perspiration The lie detectors are based in part on the increased sweat secretion under emotion Food ingestion lowers the electric resistance

The reflex may become conditioned so that it occurs at meal time even if no food is being eaten [667]

The electric resistance is high in areas which do not sweat Therefore the measuring of the electric skin resistance can be used for mapping the sudomotor innervation The areas affected by sympathectomy offer a high resistance to the passage of a very small direct current There may be variations from a few hundred to many thousand ohms within less than ¼ inch The electric skin resistance is normally lowest in a sharply demarcated area which includes both eyelids the nose the mouth varying portions of the forehead of the cheeks and of the skin under the lower lip During sleep this area becomes narrowed finally consisting of only a small margin around the mouth Similar areas of low resistance exist on the palms and the soles The patterns of areas of low

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[66] Marchio i i A Hautkra kheiten und Nerv nsystem Fortschr d Neurol Psychiat 6 7 -8 1934

[663] Marchi nini A Hautveränderungen bei nichtsyphilitischen organisch n Erkrankungen des Zentralnerv n syst ms Fortschr d N urol Psychiat 6 303-313 1934

[664] Rog r H Les syndromes sympathiques d héml udation faciale Riv di clin med 34 161 18? 1933

[665] Löblein Vas moto ische und t ophisch Störungen nach Läsion des Halssympathicus I II Monatsbl f Augenh 87 8?4 8 5 1931

[666] Wilson W C Observations Relating to the Inn rvation of the Sw at Glands of th Fa e Clin Sc 2 273 286 1936

[667] Reg lsberger H Das Electrodermatogramm und die Nahrungsrefle e des Menschen Ergebn d Inn Med u Kinderh 48 125-165 1935

temperatures greater than 3° C justifies immediate amputation of a limb The level of amputation should not show a temperature lower than 1° C below the corresponding level of the other side [2675] In diabetic gangrene the temperature may be raised therefore the skin temperature alone is not a reliable indicator for determination of the level of amputation [2675] In arteritis obliterans the feet may be warm In acute phlebitis the foot temperature is high The patient should stay in bed until the return of normal temperature [2675] Inflammatory processes increase the skin temperature in a much wider area than the immediate neighborhood of the lesion itself This seems to indicate that not so much the increased local metabolism but rather the reflex arterial dilation is the cause of the heat in an inflamed area

There is a rough parallelism between surface temperature especially of the foot and the basal metabolism so that under certain conditions the skin temperature may be used as a substitute or check for the usual basal metabolism test [675] High foot temperatures are therefore not only found in hyperthyroidism but also at the end of pregnancy when the basal metabolism is usually increased These high foot temperatures persist during lactation In general anesthesia the rise of the foot temperature indicates that the patient is asleep Primary or secondary sinking of the foot temperature indicates impending or existing shock [2680]

Morphine Wheal —If the skin is punctured with a needle through a drop of morphine solution a wheal and a surrounding flare appear Absence of the wheal indicates a block of the small arteries which feed the area as encountered in Buerger s disease If the peripheral nerve is degenerated the flare may fail to appear [681]

Raynaud's Disease

An invariable association of the peripheral vascular spasms called Raynaud s [68] disease with an internal disorder which might cause the nervous impulses leading to the attack has not been discovered In fact some analysts [683 2684] consider the absence of such a relation as a valuable criterion for the diagnosis of true Raynaud s disease However the abnormal sympathetic factor which leads to the circulatory changes cannot be denied Many modern writers on the subject deplore the rather careless labeling of a variety of vascular conditions as Raynaud s disease Raynaud himself being among the accused [2693,2694] Hunt [2685] in an effort to clarify the situation defines Raynaud s phenomenon [686] as intermittent pallor or cyanosis of the extremities precipitated by exposure to cold without clinical evidence of blockage of the large peripheral vessels and without or not more than skin deep nutritional lesions However

[2675] Bierman W The Temperatur of the Skin Surface J A M A 106 1158 116 1936

[2681] Haxthausen H Morphine Puncture A Method for D agnosing Affections in the Peripheral Arteries and Nerves Acta dermat vene eol 20 508 513 1939

[2682] Raynaud A G M De l asphyxie locale et d la gangrèn symét ique des e trémités Th se de Paris 1862

[2683] Allen E V and Brown G E R ynaud s Disease (147 Cases) J A M A 99 147- 1478 1932

[2684] Allen E V a d Brown G E Raynaud s Disea e Diagno is Am J M Sc 183 187 00 193

[2685] Hunt J H Raynaud Phenom na Qua t J Med 5 399-444 1936

[2686] Lewis Th and Pick ring G W Raynaud Disease Heart 1 3 7 366 1934

the time honored term Raynaud s disease defies eradication If one keeps Hunt s definition in mind there is no reason to abolish it since the term disease is often used for a syndrome or phenomenon of unknown cause

In the attack the skin of the fingers less often and less severe that of the toes becomes suddenly pale and cool often painful The skin temperature may be lowered as much as 16 7 centigrades (30 fahrenheit degrees) The volume of the involved part is decreased In this stage a needle prick does not cause bleed ing Cyanosis (local asphyxia) predominates in severer cases and may produce a blue, brown slate or even black color The skin becomes white on pressure but is extremely slow in taking on the color of the surrounding area after the pressure has been released The radial pulse remains perceptible during the attack The attack ends with a change of the color to vivid red caused by a violent reactive hyperemia The changes are symmetrical The sensibility is often disturbed but not abolished and the disturbances of sensitivity are like the pain ill defined and not limited to the area supplied by one nerve Anhidrosis or hyperhidrosis occurs Only in severe cases do trophic lesions like shallow ulcers paronychias and atrophy of the nails muscles and bones become ap parent In later stages the finger tips may be covered with a great number of small depressed scars If gangrene occurs, it is usually superficial and always dry Hardly ever do areas larger than an end phalanx become necrotic

The attack can be precipitated in many cases by immersion of the hand in cold water or by exposure to cool air or by chilling of the body by cold drinks [2687] Cold is the most important immediate cause although emotion also plays an important part in the precipitation of the attacks [2686, 2688, 2689] The trouble is predominantly found in young and middle aged women The prognosis is usually good with respect to life but the attacks may recur over many years The pathogenesis of the phenomenon is still controversial Raynaud and many others after him believed that an abnormal vasomotor tone was the main patho genetic factor Lewis (see Hunt [2695]) produced much physiological evidence to the effect that the vasomotor tone was in order but that there was a local fault in the medium sized digital arteries [2690] Several autopsies on cases having had the disease for long periods of time have not revealed any changes in the ar teries [2691, 2692] but a few instances of endarteritic alterations have been observed (Kolisch after Mucha[2693]) Microscopic changes in the sympathetic ganglia and other nervous centers are on record [2694] The vascular as well as the neural, findings are not uniform and some are probably secondary The capillaroscopic picture during the attack is characterized by the empty and seemingly absent

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[2687] Johnson C A Raynaud s Diseas 2 Cases Surg Gynec & Obst 72 889 907 1941

[2688] Craig J D Raynaud s Disease Psychogenesis Dis Nerv System 5 14 146 1944

[2689] Mufson J Raynaud s Diseas Ann. Int Med 20 28 238 1944

[2690] Hyndman O R and Wolki J Raynaud Disease Vascular—not Sympathetic—Disease Am Heart J 23 535-554 1942

[2691] Dannigel H Ein Fall von Raynaud scher Krankheit mit Obductionsbefund Diss Freibu g i B 1933

[2692] Leriche R and Fontaine R Su la nature de la maladi de Raynaud Pres e méd 193? II 19 1 19 5

[2693] Mucha V Die Raynaud sche Krankheit Ha db f H u Gk 6 2 ?73-300 19 8

[2694] Pallasse Dechaume J and Arnaud Lésions de la chaine sympathique dans la maladi d Raynaud Lyon méd 1931 II 117 124 Zbl 40 71

capillaries and the constricted arteries The spastic picture is followed by atonic dilatation in the asphyctic stage but both spasm and atonia may be seen simultaneously[2690] The capillaroscopic changes exceed the macroscopically changed areas There can be no doubt that vasomotor stimuli play an important part This is best demonstrated by the immediate success of surgical removal of the sympathetic fibers or ganglia through which the vasomotor stimuli must pass After sufficiently extensive sympathectomy by one of the many suggested methods (Review and Methods see Homans[2694] and Adson[2695]) the vascular paralysis which follows the operation leaves the fingers flushed and no attacks occur as long as the sympathetic fibers do not regenerate

The associated conditions which can be found in patients with Raynaud s disease are most often of functional character In 24 per cent of a series of 147 noncomplicated cases psychoneurosis or neurasthenia was obviously a feature[2684] Syphilis arteriosclerosis and a number of rare diseases[2653] have been found in connection with Raynaud s syndrome Linenthal[2696] described 5 cases with pulmonary fibrosis A rare finding is a cervical rib If this anomaly is unilateral the attacks are unilateral but intermittent in spite of the continuous cause[681 685 697] Menopause[699 2701] sclerodactyly[2685 2704] arsenical[2685] and copper poisoning[703] are other rare combinations Lewis and Landis[2704] make use of the combination with sclerodactyly to support the arteritic theory of Raynaud s disease Sellei[2705] separates sclerodactyly (acrosclerosis) from Raynaud s disease as well as from scleroderma Combination with tetany[706] and calcifications[70 2708] have caused speculation about a parathyroid etiology Subtotal parathyroidectomy has not proved successful[1854]

Treatment —Since the paralytic hyperemia does not last the enthusiasm about the surgical approach has somewhat abated so that lately medical management has again been said to give equally satisfactory results Johnson[687] stresses prevention of attacks by avoiding the thing that precipitates them

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[2695] Adson A W Raynaud s Disease *Results of Sympathectomy* S Clin North America **17** 1051 1061 1937

[2696] Linenthal H Raynaud s *Disease Pulmonary Fibrosis* 5 Cases New England J Med **227** 433 436 1942

[2697] Lenèque J and Lelong M Côte cervicale bilatérale Syndrome de Raynaud unilateral Bull et mém Soc nat de chir **61** 1073 1083 1935 Zbl **83** 464

Cassirer H Vasomotorisch trophische Neurosen ed 2 Berlin 1912 S Karger

[2699] Wirth Raynaudsche Krankheit und Urticaria chronica papulosa *Zbl* **14** 29 1914

Borneo A Raynauds Disease in Menopause Wien med Wchnschr **75** 970 71 1925

[2701] Berger G Gefässtörung der Hände im Klimakterium Zbl **40** 577 1930

[2702] Bercow R G and Poppel M H Raynaud s Disease Interstitial Calcinosis Circumscripta Associated With Scleroderma Radiology **29** 96 98 194

[2703] Simon A Ueber Kupferschädigungen und die Beziehung zum Raynaudschen Symptomenkomplex Arch f Gewerb path **2** 71 80 1931 Zbl **38** 508

[2704] Lewis T and Landis E M *Raynaud s Disease Special Reference to Arteriolar Defects and* Scleroderma Heart **15** 329 350 1931

[2705] Sellei J Akrosklerose und Raynaudsche Krankheit Arch f Dermat u Syph **173** 35 -356 1936

[2706] Borowsky M L Die Pathogenese der Raynaudschen Krankheit Deutsche Ztschr f Nervenh **114** 232 254 1930

[2707] Rhee G van Raynaud s Disease With Calcareous Deposits Arch Dermat & Syph **29** 930 1934

[2708] Walker R H Calcification in Raynaud Disease Proc Roy Soc Med **27** 6 7 628 1934

Secondary anemia should be treated Pancreatic extracts and thyroid[2709] have been advocated Paraffin baths also have given considerable relief The attack is best treated by immersion of the hands into warm not hot water

Erythromelalgia (Weir Mitchell's Disease) —*This* syndrome features attacks of severe pain redness and swelling usually of the feet Hyperhidrosis is usually present in the involved area The paroxysms are sometimes pre cipitated by exposure to warmth and depression of the limb Though occasion ally associated with Raynaud s disease it exhibits in many respects the opposite phenomena Among a great number of occasional associations the connections with polycythemia (see there) Bence Jones albuminuria and neurasthenia must be mentioned [66, 663, 710, 71]

Acrodynia (Feer's Disease, Pink Disease)

Acrodynia though probably known and described in France under this name[2713, 714] more than a century ago has become better understood and more sharply defined only during the present century The names of Swift[2715] Selter[716] and particularly Feer[2717] after whom the disease is often named designate some of the many authors who have been concerned with it

The disease affects small children almost exclusively According to Feer[2717] the onset is insidious The children are listless irritable sometimes vicious and do not care to play The facial expression is frowning unchildlike weary so that the experienced physician can make the diagnosis on the physiognomy alone especially if the contracted eyelids are added to the picture The sleep is disturbed and the appetite lost Fatigue and gradually developing motor disturbances like unwillingness or inability to walk or stand a bizarre and per sistent jackknife like position in bed with the head between the feet general flaccidity of the muscles without atrophy frequent light tremor and other nervous symptoms are essential features Other important signs are increased pulse rate and blood pressure high basal metabolism high blood sugar and high sedimentation rate The temperature may be normal but fever has often been observed in the beginning and during complications Monothermia is some times a remarkable feature Encephalitic features resembling parkinsonism have been observed[2718]

[2709] Ipsen J Zwei Fall von d Raynaudschen Krankheit mit Untersuchungen d r Art ri n Acta chir Scandinav 71 48 -49 193 Zbl 45 474

[2710] Hirschfeld R D Erythromelalgie Handb d H u Gk 6 60 ?73 19 8

[2711] Lewis Th Clinical Observatio s and Experim nts Relati g to Bur ing Pain in the Extr mities and to so-called Erythromelalgia Clin Sc 1 175 211 1933

[2712] Brown G E Erythromelalgia and Other Disturbances of the Extremities A compa ied by Vasodilatation and Burning Am J M Sc 83 468-495 193?

[2713] Chardon De l acrody ia ou épi l mie qui a r gné à Paris d puis 18 8 R v méd franç et étrang 3 51 1830

[2714] Péhu M Ac odynie d autrefois t acrod d aujourd hui Bull Acad d méd Paris III 111 547 553 1934

[2715] Swift H Erythroedema Lancet 1 611 1918 (Lette to th editor)

[2716] Selter I Acrodynia 42 Cases Arch f Kinderh 80 44 5 19 7

[2717] Feer E Acrodynia in P t rman s Tra slatio of Pfaundler and Schlossman th Dis ases of Children Vol III Philad lphia 1935 J B Lippincott Co pp 435-445

[2718] Morquio L Ueber ein n Fall von Infantil r Akrodynie Arch de pediat d Uruguay 3 10, 119 1932 Zbl 43 58

Acrodynia takes a protracted course over many months Complete recovery is the rule Recurrences are rare[2719] The mortality rate among 200 cases in Australia was 3 per cent[27 0] when the patients were treated in their own homes but rose to 30 per cent under hospital care with the danger of intercurrent infection Higher mortality rates have also been observed[2717 27 1 27 4]

Dermadromes —Dermadromes occur frequently[27 5] and may at times completely dominate the picture From the start the skin feels cold clammy and flabby *Sweating* to a degree which has its equal only in miliary fever weakens the patient and causes thirst Sparse or copious miliaria rubra[2726] or micropapular follicular eruptions soon follow the excessive sweating The skin between the miliary papules may be diffusely bluish or red the feature from which the



Fig 341 — Acrodynia Peeling (Patient of Dr S F Kohn)

name pink disease was derived (Glubbe after Crawford[2724]) The papules may enlarge and become scaly and eczema like Cases of acrodynia have often been mistaken for eczema as long as the other important symptoms had been overlooked In typical cases of acrodynia the macerated skin soon peels in large

[2721] Péhu M R cidivations of Infantile Acrodynia Schweiz med Wchnschr 71 1207 1208 1941
[2722] Wood A J and Wood J Pink Disea Brit M J 3893 527 531 1935
[2723] Ratcliffe T A Acrodynia J Ment Sc 87 545 571 1941
[2 2] Bode H S Die Feersche Krankheit im Licht der Dermatologi Arch f D rmat u Syph 167 15-46 1932
[27 3] Fo rster H R E ythredema Polyneuritis Arch Dermat & Syph 12 17 3 1925
[2724] Crawfo d S Juvenile Acro lynia Eleven Case A ch Dermat & Syph 26 215 37 1932
[2725] Audeoud H and Boissonnas L 18 Cases of Acrodynia Rev méd de la Suisse Rom 59 785 794 1939
[2726] Fessler A Hautveränderungen bei der Feer schen kindlichen vegetativen Neurose (Selter Swift Feer sche Krankheit) Arch f Dermat u Syph 173 83 290 1935

flakes or in smaller circular patches The *peeling* is particularly marked on the hands and feet so that it may be mistaken for scarlatina Besides rashes from sweating and repeated crops of macular urticarial or multiform exanthems may occur especially on the mesial areas of the trunk[27??] sometimes also on the extremities Itching is most violent Scratching and possibly trophic disturbances may cause pyodermic ulcerative and necrotic complications Bed sores occur quite frequently The teeth may become loose and fall out Geographic tongue is a frequent feature[2727] Salivation frequently adds to the discomfort, and may outlast the excessive perspiration The hands and feet show a characteristic purplish pink erythema The nose and cheeks may also be red

The *hair* becomes dull and is often shed The young patients often like to pull the loose hair out and the vertex frequently becomes bald

Diffuse and focal inflammatory changes have been found in the sympathetic system so that the disease has been explained as a disorder of the vegetative nervous system and the term *pansympathitis* used [717] [7] [731]

The nature of the anatomical changes in the cerebrospinal system are still controversial [73] [734] Several neurologists believe that encephalitis influencing the vegetative centers of *the thalamencephalon* plays a part In the skin hyperkeratosis parakeratosis intracellular edema [724] and inflammatory infiltrations in the stratum subpapillare with damage or loss of the elastic fibers and vasodilatation are microscopic features Bode[2735] described eosinophile bodies in the prickle cell layer surrounded by lamellated cells

The disease is probably an infection of the autonomic nervous system though neither microbes nor positive animal inoculations have been demonstrated However local accumulations of cases a few familial cases [2736] [2737] the seasonal increase in winter and spring and the existence of fever inflammation and apparent but not invariable immunity after recovery make the infectious etiology attractive Endocrine [2738] toxic avitaminotic or chronic neurotrophic [739] hypotheses have been suggested An interesting argument in favor of the in

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[?27] Péhu M Dechaum J and Boucomont J L Ac odyni infantile Anatomie pathologi que Bull Acad de méd Paris III s 113 818 823 1935

[2729] Péhu M a d Boucom nt J L acrodyni I fantile Atti 15 Congr ital Pediatr pp 587 588 1934 Zbl 52 2

[272] Péhu M Dechaume J and Boucomont J Sur l acrodynie infantile Rev franç de pédiat 12 39 2 6 ?77 310 589-607 936 Zbl 64 333

[?] ou iquand G Dechaum J and Sedallian P Tentatives d expérimentation sur l acrodynie encéphalite spontané du lapin Ann de méd 41 85 99 1937

[?] Clément R Formes atypique de l acrodynie Pre méd II 1607 1610 1935

[273] Wolf I J and Davison Ch Acrodynia J Pediat 4 498-506 1934

[2733] Deam r W C and Biskl d G R Acrodynia Am J Dis Child 48 13 6-1335 1934

[2734] Bellocq G Ph and Mey R Étude Cliniqu et A atom Pathologique d une Fo me grave d acrodynie Rév franç de pé iat 8 495-508 1932

[2736] Blechmann G Montlaur H and Leconte A L ac odyni maladie contagi use? P ésentation de deux frères acrodyniques Bull Soc de pédiat de Paris 31 135 137 1933

[2737] Blechmann G and Leconte A Acrodynie familiale (Trois enfants) Bull Soc de pédiat de Paris 33 5 0-5 3 1 ?35

[2738] Rietschel H Zur Pathogenese der Feerschen Krankheit Deutsche med Wch schr 193 I 723 725

[273] Bode H C and Scheuff A Feer s he Krankheit Zbl 43 ?51 ?5? 1932 1933

fectious etiology is the epidemiological and clinical relationship to acute miliary fever which has similar geographic distribution and symptomatology Its course however, is much more acute and dangerous

No specific treatment has been found Feer advocates high doses (2 mg daily) of atropine Ultraviolet light has also been found effective

CHAPTER XXXVIII

DISORDERS OF THE NERVOUS SYSTEM

Neurocutaneous Diseases

The common ectodermal origin of essential parts of the skin and the nervous system is reflected in some diseases which affect both systems at the same time and in the same or at least in a comparable manner These diseases have been called neurocutaneous diseases or congenital ectodermoses The group comprises von Recklinghausen s disease (neurofibromatosis) Bourneville s disease (tuberous sclerosis of the brain) and various types of angiomatosis of the brain eye and skin

Von Recklinghausen's Disease —Von Recklinghausen s disease is because of its frequency by far the most important member of the group The dermadromes tumors and pigmentations are the most common and striking manifestations of the disorder The tumors may appear as fibromas and neurinomas which cannot always be distinguished clinically Particularly the nature of small tumors may be doubtful In large soft fibromas a wormlike, neurinomatous plexus may be palpable indicating the ill defined clinical borderline between the two types of lesions

The *fibromas* are usually soft (fibromata mollusca) and indolent rarely firm They may vary in number from a few to several thousand There does not seem to be any site of predilection although the large fibromas seem to arise more often on the eyelids the buttocks and the labia majora The tumors may range from pinhead sized nodules to gigantic growths weighing more than 80 pounds If such large tumors involve an extremity the term elephantiasis mollis is often used The fibromas may be flush to or raised above the level of the skin and the base may be thin or wide the tumor accordingly appearing pedunculated or sessile The covering skin is most often normal in appearance but sometimes it is pigmented leathery and warty A peculiar type is represented by fibromas which give the appearance of an empty bag of scrotum like wrinkled soft thick skin (pachydermatocele) Such flabby tumor formations may be seen on any part of the body surface Trauma may change them into large and troublesome hematomas The surface of the fibromas may show comedos or local hypertrichosis The palms and soles are seldom involved Spontaneous involution is very rare [2740]

The *neurinomas* (neurofibromas) represent the second type of Von Recklinghausen neoplasms In typical instances they are much firmer than the fibromas and tender on palpation or sometimes spontaneously painful They are often spindle shaped or show their neurogenic origin by palpable worm or

[2740] Saalf ll E and Saalf ld l Hautmyome Reckll ghau n et Han ib d H u Gk 12, 2 55 191 193

plexus like structures The neurinomas may develop anywhere along peripheral nerves or in the central nervous system and they too may reach very large sizes

In one of the cases presented by Jones Jr and Hart[2741] the mass grew slowly from a small buttock tumor to a size which exceeded half of the entire body of the 36 year old emaciated man



Fig 342 —Von Recklinghausen s disease

The *pigmentary* lesions of Von Recklinghausen s disease occur as large and small spots H W Siemens[2742] emphasizes that the large spots differ from the ordinary smooth pigmented nevi Their edges are smooth and their color is yellowish brown while the true nevi spili have a more jagged contour and an olive shade The large Recklinghausen spots range from fingernail to palm size the larger ones often being oval shaped and arranged in the direction of the cutaneous lines of cleavage Their color is best characterized by the often used term cafe au lait The small spots resemble freckles but their distribution is even and

[2741]Jones R Jr and Hart D Multiple Neurofibromatosis Ann Surg 110 916 939 1939
[2742]Siemens H W Clinical and Dermatologic Studies on Recklinghausen s Disease Arch f Dermat u Syph 150 80 103 1926



Fig 343 —Von Recklinghausen s di as



Fig 344 – Von Reckli ghausen s disease Empty po h (From Hart Ann S rg)

is not influenced by exposure to light [2742] The small spots may be innumerable Pigmented spots of both kinds are hardly ever missed They may precede other skin manifestations by many years Ordinary and unusual nevi e g the so called bathing trunk nevus hemangiomas and the nevus anemicus have been noticed in a number of instances [2741 743]

The systemic character of Von Recklinghausen s di ease manifests itself in the multiplicity of organic involvements Abdominal intestinal [741] intra



Fig 34 —Von Recklinghausen s lisease Giant fibroma i t rsperse l with pseudo-cy tic lesion



Fig 346 —Von Recklinghaus n s di ea Empty pouche

[2742] Wakel y C P G an l W ber F P Gen alized N u ofibrom to i With Naevus Anaemicus Internat Cl n 1 S r 46 144 147 1936

[27 4] Barton A D and Inglis I Neurofibromato i With Both Cuta u and Visceral Lesions J Coll Su g ons Australasia 9 397–40 1931 Zbl 39 55

pleural [745] and mediastinal [746] neurofibromas as well as sciatic nerve tumors illustrate some of the many rare localizations Of greater importance are the neurinomas of the central nervous system and of the intracranial nerves A considerable part of the meningiomas of the tumors of the spinal cord of the cerebello pontine angle and of the acoustic nerve belong here [630 274 51]

The symptomatology of these central tumors depends on their location The central neurinomas are usually not malignant although their site may make them extremely dangerous

Perhaps of greater practical importance than the relatively rare central lesions are the involvements of the skeleton Here too the site is more im



Fig 317—Von Recklinghausen s disease E ormou neurofibroma of the hip (F om Hart Ann Su g)

portant than the size or number of the lesions which cause cystic destruction and peculiar irregularities in the growth of some long bones as a sequel to epi physeal or shaft lesions during the growing age [2741] Kyphosis may be an early symptom even before skin lesions are noted Kyphoscoliosis has been observed

[745] Canigi ni T Die intrathorak len Neurofibrom Röntgenp ax 3 .14 .19 1931
[746] Maksim O Heathorne J O and All bach H K N urofibromatosi With Malignant Thoracic Tumor and Metasta is in a Child Am. J Dis Child 57 381-390 1939
[747] Antoni N R F Rück nmarkstumo en und Neurofibrom Anatomi und Embryogenese München and Wiesbaden 19 0 J F B rgmann
[748] Mosbacher F W Recklinghausensche Krankheit u d Tumo cereb i P ychiat neurol Wchnschr 1931 II 411-418
[749] Mosbach r F W Recklinghausen sch Krankh it Fortsch d N urol Psychiat 3 220 1931
[750] H I moortel J Jr and Thie pont R Tum urs bilatérales de l acoustique dans la n urofibromatose J belge de n urol et d psychiat 33 7 0-785 1933
[751] Foerster O a d G g l O Z ntral diffuse Schwan ose bei Recklinghausen scher Krankheit Z N ur 151 1 16 1934

in as many as 43 per cent of some series[275] Pseudarthroses of the legs cystic destruction of the hip bones[2753] compression of the spinal cord[2754] and osteo malacia[2755] represent some of the typical skeletal phenomena Moderate acro megaly[2756] cutis verticis gyrata[2757] Frohlich's syndrome[2758 2759] adrenal symp toms[2760 61] vagus tumor[2 6] high blood calcium and potassium[2763] and many other endocrine features[2 64] have been recorded without leading to a well founded endocrine theory of the pathogenesis of Von Recklinghausen s disease[2761] In this connection the unfavorable influence of puberty and pregnancy on the pro duction of tumors must be mentioned Psychic anomalies including all degrees



Fig 348 —Von R cklinghausen s disease Large and small pigmented spots

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[2752]Stalman A Nerven Haut und I nochenveränderungen bei der Neurofibromatosis Reckling hausen Virchows Arch f Path Anat **289** 96-126 1933

[2753]Richter W Neurofibromato is Recklinghau en mit cystischen Veränderungen in d n Hüft-gelenkknochen Zbl **44** 37

[2754]Miller A N urofibromatosis With Reference to Skeletal Changes Compression My litis and Malignant Degene ation A ch Surg **32** 109 122 1936

[2755]Cole H N and Driver J R Von Recklinghausen s Disease Arch Dermat & Syph **22** 753 1930

[2756]Blotevogel H Die Charakterbildung der Neurofibromatose (Recklinghausen) Dermat Wchnschr *1933 I 361 368*

[2757]Rajka E Pachydermie vo tic lle (Cutis verticis gyrata) Morbus Recklinghausen Zbl **44** 15 1933

[2758]Rusakova B Zur Frage der endokrinen Anomalien bei der Recklinghau enschen Krankheit Russk Vest Dermat **9** 2 1931 Zbl **39** 315

[7] Obstände E Zur Frage der Dystrophia pluriglandularis neurofibromatosa Wien med Wchnschr 1931 I 638 639

[27] Rosenthal D B and Willis R A Association of Chromaffin Tumours With Neurofibroma tosis J Path & Bact **42** 599 603 1936

[2761]Levin O L and Beh man H T Neurofibromatosis—Elusive Manifestations and Internal Relations Arch Dermat & Syph **41** 480-50 1940

[2762]Siebner M Vagustumor bei Recklinghausenscher Neurofibromatose Deutsche Ztschr f Chir **237** 63 79 1932

[2763]Mariante Th and Maciel P Recklinghausen s Disease and Ca Metabolism Rev radiol e clin **1** 332 341 1932 Zbl **43** 533

[2764]Freund H Ueber endokrine Störungen bei Recklinghau enscher Krankheit Arch f Dermat u Syph **166** 128 142 19 9

of feeble mindedness and frank psychosis [75 765 2767] are common Hebra believed "that all patients suffering from fibroma molluscum were mentally retarded individuals In a modern series [748] about one half of the patients showed mental deficiencies

The patients afflicted with Von Recklinghausen s disease often have a characteristic melancholic or bored facial expression which Rille [768] partly ascribes to changes in the facial skin The eyes and ears participate in the morbid process in many ways There may be enormous tumors of the lids[2 69] and of the



Fig 349 —Von Recklinghaus n s di as Small pigmented spot and la ger pigmented moles The patient is only 2_ years old th refo le ion mostly small and not too numerous (Courtesy Wisconsin G neral Ho pital)

[2765] Hubble D and Rog rson C H Anxiety Alopecia Areata Neurofibromatosis Auri ular Fibrillation Case Brit M J 1 486-488 1944

[2766] Sostakovic V Sympt matologie der Reckli ghau ensch n Krankheit Obozr P ichiatr 4 167 173 1929 Zbl 36 77

[2767] Woringer F Maladi de Recklinghausen Bull Soc franç de dermat et yph 39 1510 1512 1932

[2768] Rille Der G i ht ausd uck ein eies Kenn ich n des Morbus Recklinghausen Dermat Wchns hr 1935 II 143_-143?

[2769] Knapp A A Von R cklinghaus n s Dis ase Ca With Involvem nt of Left Ey lids J A M A 100 494-495 1933

sclerae,[770] buphthalmos, changes of the retina and of the optic nerves or their surroundings,[2771] and tumors.[2740]

Deafness from bilateral acoustic nerve tumors and other nervous disturbances of hearing are well known and sometimes demonstrable by roentgenographic examination of the petrous bone.[277, 2772]

The disease is hereditary though certain factors may be necessary to make the hereditary character manifest. The trouble has been seen as a concordant feature in homozygotic twins,[7, 6, 2774, 775] occurring in six generations[2772] and in as many as four siblings.[776] Among 115 children of Recklinghausen patients 43.5 per cent were afflicted.[2777] H. W. Siemens characterizes the inheritance of Recklinghausen's disease as an irregularly dominant one. Solitary cases without apparent familial connection are not rare. Both sexes are equally affected.[2740] The tendency to malignant degeneration of Recklinghausen tumors may be familial (Hockstra after Mosbacher[43]).

The syndrome occurs in many degrees of severity. Within one family cases with all types of manifestations may be seen together with cases whose only symptoms may consist of some pigmented spots without tumors. Generally, the term "formes frustes" is applied to cases with less than the four types of dermadromes: the large and small pigmented spots, the fibromas and the neurinomas. Apparently abortive cases showing very few lesions may still become severe.[2778]

The disease may be connatal but commonly comes on gradually.[2779] At certain periods, however, like puberty, pregnancy and the menopause and after infections like typhoid and mumps the rate of appearance of new symptoms may be stepped up. Since the lesions only come and do not go, older patients usually have more than younger patients.

The course of the disease has already been indicated. In advanced age, the cases often become more progressive and changeable.[2780]

The life expectancy is generally favorable but may be entirely changed by complications, particularly of the nervous and skeletal systems. Sarcomatous degenerations of (see Charache[781]) tumors occurs in about 10 per cent,[740] prob

[2770] Mamoli L. Caso di morbo di Recklinghausen con manifestazioni endocraniche e rara localizzazione epibulbare. Atti Congr Oftalm pp 663-6 5 1932 Zbl 45 64

[2771] Webe F. I. and Bode O. B. Recklinghausen's Neurofibromatosis With Unilateral Buphthalmus and Multiple Changes in the Face and Skull. Proc Roy Soc Med 27 638-640 1934

[2772] Gardner W. J. and Turner O. Bilateral Acoustic Neurofibromas. Arch Neurol & Psychiat 44 76 93 1940

[2773] Hableín G. W. Pendergrass E. P. and Widmann B. P. Roentgenographic Findings in Neurocutaneous Syndromes. Radiology 35 01 7 7 1940

[2774] Le rs H. Recklinghausensche Krankheit und cerebrales Syndrom bei einem eineigen Zwillingspaar. Ztschr f menschl Vererb u Konstitutionsl hre 19 7 1 730 1936

[2775] Loftis E. L. Neurofibromatosis in Identical Twins. Arch Dermat & Syph 42 657 1940

[2776] Caland A. 4 Brothers With Neurofibromatosis. Brit M J 2 190 1941

[2777] Preiser S. A. and Davenport C. B. Multiple Neurofibromatosis and Its Inheritance. Am J M Sc 156 507 540 1918

[2778] Gaté J. and Cuilleret P. Un cas de maladie de Recklinghausen. Bull Soc franç de dermat et syph 40 355 358 1933

[2779] Andrews G. C. Von Recklinghausen's Disease. Arch Dermat & Syph 24 685-686 1931

[2780] Sharpe J. C. and Young R. H. Recklinghausen's Neurofibromatosis 31 Cases. Arch Int Med 59 299 193

[2781] Charache H. Multiple Neurofibroma With Sarcomatous Transformation and Skeletal Involvement. Arch Dermat & Syph 40 185 191 1939

ably even less frequently The patient dies with Von Recklinghausen s disease but rarely of it [778]

The microscopic structure of the neurinomas shows bandlike zones of parallel elongated nuclei alternating with zones of parallel thin fibers without nuclei Sometimes the fibrous part is transformed into a dense finely reticular structure with fusiform and anastomosing cells Mitoses are very rare The growth generally has all the characteristics of a benign neoplasm Most pathologists believe that the neurinoma stems from the cells of the sheath of Schwann thus being of ectodermal origin The theory of mesodermal nature is defended by a minority an important argument being the transition into sarcomas [783 2785]

No satisfactory method of treatment is known

Many authors advise against inadequate surgical removal of tumors because of the danger of sarcomatous degeneration [667] The removal of one sarcomatous growth may be followed by a distantly located sarcomatous transformation [2781]

Tuberous Sclerosis of the Brain —(Bourneville s Disease) This is a congenital progressive and often familial condition It is characterized by epileptic seizures of varying types mental deficiency varying from queerness or feeble mindedness to severe idiocy by eye disorders and dermadromes The triad of adenoma sebaceum epilepsy and mental deficiency is called epiloia The brain lesions are whitish, relatively firm well circumscribed plaques and tumors They are found in varying parts of the cortex as well as in the ventricles In the lesions the nerve cells are widely destroyed or damaged by neuroglial proliferation and other processes among which a certain type of large cell and a tendency to calcification are prominent features The latter and frequent hydrocephalus are radiographically demonstrable [773] Tumors resembling hypernephromas rhabdomyomas of the heart and a variety of other neoplasms may be found A high basal metabolism [786] gynecomastia precocious puberty [787] congenital malformations [2788 2789] and neurogenic mulberry shaped tumors of the retin [790] have been described in association with tuberous sclerosis The disease becomes manifest in early childhood and runs a slowly progressive course The majority of the patients die before the age of 25 years (Bielschowsky and Gallus after E Guttmann[2630])

[2782] Harbitz F Multiple Neurofibromatosis A ch Int Med 3 3 -6 1909

[2783] Cushing H and Eis ndrath L M ingiomas Springfl I1 Ill 1938 Charles C Thomas

[2784] Or echowskl K Neurf ome Handb d H u Gk 12, ? 193

[2785] McNalry D J and M tgome y H Cutaneous Tum rs of von Recklinghausen Disease Arch D rmat & Syph 51 384-390 1945

[2786] Kreyenbe g O Delbanco E and Haach F Tuberöse Skl rose und Ade oma s bac um Z Neur 128 ?36- 56 1930

[2787] Watrin J M Igna t P and Weille R Case of Bourn vill s Tube ou S l rosis and Symmetrical Fibromatou Nevi of Face An d d mat et yph 10 644-6 5 1939

[2788] Feriz H Fin B itrag zu Histopathologi d tuberös n Skl ros Virchows Arch f path Anat 278 690-769 1930

[2789] Lufs H U b r len Frbgang d r tuberösen Skl ros zugl i h in B itrag ur klinischen Diagnostik und Histopathol gie diese kra kh it Z N ur 144 562 58 1933 711 45 349

[2790] Van Der Hoeve J Eye Symptom in Phacomat ses Tr Ophth Soc U Kingdom 52 380-401 193?

The disease has frequently been encountered in families sometimes in three generations[2789 2791 793] and occasionally together with manifestations of Von Recklinghausen s disease[748 279? 2794 798] indicating the relationship of these two neurocutaneous syndromes which seem to be caused by unknown factors acting on the ectoderm



Fig 350 —Tuberous scl ro is (epiloia) Ade omata s bac a in typical d t il ution along the nasolabial folds and on the ch n (From Good G K and Carb J Arch D mat 1943)

Dermadromes —*The best known derm idrome of tuberous sclerosis is the adenoma sebaceum* of the face This dermatosis consists of more or less raised discrete hemispheric papules which are mainly arranged in the neighborhood

[2791]Koenen J Ei e familiä hereditäre Fo m von tuberöser Skleros Acta p ychiat **7** 813 821 193

[792]Koenen J Ei familiäre h ditäre Form von tub rö er Skl ro e Nede l tijdschr v geneesk 1931 I 731 738

[27 3]Borreman Dyckmans and Van Boga rt Form s hérédof miliale de la sclérose tubereuse J belge d neurol et de psychiat **33** 713 746 1933 Zbl **48** 406

[794]Werthe Mo bu Pringl Mo bus Recklinghausen und tube öse Hi nsklerose Zbl **35** 60 1931

[2795]Butte worth T nd Wil on M Jr Tub rous Scle osi Dermatological A pect Arch Dermat & Syph **43** 1-41 1941

[2796]Bychowski Z Tub rö e Skl rose Wars aw Cz lek **8** 4 9-463 1931 Zbl **39** 186

[2797]Mukai J Naevus s ba Acta de mat (I yoto) **17** 453-475 1931 Zbl **39** 554

[2798]Fuhs Naevus Multiplex Pringle Zbl **45** 15



of the nasolabial and mental folds The symmetry is marked The size of the individual lesions ranges from a few millimeters in diameter to almost a centimeter the larger lesions being flatter and usually situated in the center of the group The papules may vary in color and firmness In the so called Balzer type the papules have the color of normal skin in the Pringle type they are soft and red and in the Hallopeau Leredde Darier type they are small and very firm[2799]



Fig 353 —Tuberous sclerosis Large fibromatous nevoid growth of the scalp (From Good G K and Garb J Arch Dermat 1943)

The pathological differences are explained by the prevalence of the sebaceous glands the vascular elements or the fibrous stroma Spontaneous regression has been observed in some cases but this is not the rule The three types may be seen together[743]

Nevoid slow growing pigmented *plaques* of a size which may cover for example the entire temporal area and keratofibromatous leather like plaques sometimes reaching palm size have been described[279, 800, 801] The lumbar region is a favorite site for such nevoid plaques and similar growths The plaques show

[279] Dobkévitch S Adénomes Nouvelle Pratiqu D rmatol Vol VI Paris 1936 Mas on & Cie
[280] Sachs M D and Shaskan D A Tub ous Skleros s Am J Roentgenol 52 35 39 1944
[281] Furt L Tub ö e Scl rose Hautverände ung n D rmat Wchnschr 1934 I 357-365

pathologic changes similar to the adenomatous papules They are not of the same diagnostic importance as the adenoma sebaceum [737, 809]

Slow growing multiple para ungual fibromas of small pea size especially of the toes [803] have recently become known as a derm idrome of tuberous sclerosis The lesions which have a keratotic top bleed easily and may become troublesome These tumors find their mucosal equivalent in lobulated fibromas of the gums [793–803] The nail substance may appear thickened or grooved lengthwise [804]

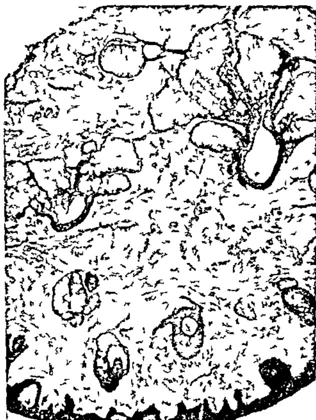


Fig 354 —Ad noma bac um (Courte y Divi i n of D rmatology D pa tm t of Medicine University of Chicago)

Lipomas syringocystadenomas and some of the skin lesions known to occur in Von Recklinghausen s disease have also been found occasionally in tuberous sclerosis

Frequently the adenoma sebaceum makes its appearance in the first decade of life [2, 95] possibly stimulated by the same hormonal factor which causes the development of the sebaceous glands

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[793] Van Bouwdijk Basti anse F S Form familiale de sclérose tubereuse J belg de Neurol et d psychiat 33 697 71 1933 Zbl 48 408

[803] Kurtz L Tuberös Sklerose mit Hauterscheinung (subungual Fibrom an Fi g rn und Zehen Rosacea des Gesichtes und lymphangi ktatisch Fibrom an der Gingiv) Zbl 43 30

[804] Loos H O N gel Haut und Allg m in rkranku g n Med Klin 36 4 9-491 1940

Angiomatosis cerebri —Hemangiomas of the brain are frequently[2773, 2805, 2806] associated with vascular nevi of the face While the nonactive nevus like hemangiomas are apt to be found in the cerebrum the growing angioblastomas usually develop in the cerebellum Only the former seem to have related skin lesions while both develop eye manifestations though of different types The nervous symptoms usually start very early sometimes during the first months of life [2807, 2808] Contralateral jacksonian fits vertigo tremor disturbances of the gait and hemiplegia [2809] are the most obvious symptoms Idiocy has also been observed [2807] The brain lesions may calcify and thus produce roentgenologic pictures[2773, 2810] consisting of whorls and sinuous deposits in the gyri of the frontal and temporal lobes Asymmetry of the face[2773, 2805] may accompany the unilateral brain changes

The accompanying vascular nevi mainly occupy the face They seem to be more often unilateral than bilateral They are large even enormous[2811] single



Fig 355A —Fibroma of the nail bed in tuberous sclerosis and adenoma sebaceum (Courtesy Division of Dermatology Department of Medicine University of Chicago)

[2805] Krabbe K H Facial and Meningeal Angiomatosis With Calcifications of the Brain Cortex Arch Neurol & Psychiat 32 737 75 1934

[2806] Lufs H Ueber heredofamiliäre Angiomatose des Gehirns und der Retina ihre Beziehungen zu einander und zur Angiomatose der Haut Ztschr f d ges Neurol u Psychiat 113 651-686 1928

[2807] Meyer F Gesicht hauthämangiom und Gehirnrankenangiom Monatschr f Psychiat u Neurol 92 94 208 1936

[2808] Schaefer W Ueber einen Fall von halbseitigem Gehirn und Hauthämangiom Monatsch f Kinderh 50 35-44 1931

[2809] Kreyenberg G and Halting I Hauthämangiom mit Rankenangiom des Gehirns und Hydrophthalmus Z Neur 152 751 7 6 1935

[2810] Schwarz C W Vascular Tumors and Anomalies of the Skull and Brain From a Roentgenological Viewpoint Am J Roentgenol 41 881 900 1939

[2811] Ironside R and Hill D Cutaneous Naevus With Buphthalmos and Epilepsy J Ment Sc 87 631-634 1941

or multiple telangiectasias of port wine stain or tumor type sometimes involving the oral mucosa and even the pharynx [2812]

The nevi are often, but not necessarily on the side of the hemangioma of the brain [2813, 814]

Besides the telangiectatic lesions nevus anemicus has been recorded in several instances [2814] Pigmented nevus of one side of the face and ipsolateral glioma has been seen by Meirowsky [815]



Fig 35 B —Tuberous sclerosis Fibromas of the nailbeds with grooving of the nail (From Noon Z B Arch De mat 1944)

Heredity is an etiological factor [2816] Occasional combinations with the other neurocutaneous diseases have been reported [2817, 66, 663]

The term Parkes Weber s syndrome is sometimes used for the combination of cerebral and cutaneous hemangiomas with epilepsy and idiotism

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[2812] Tyson H H Nevus Flamm us of the Face an l Gl be Associated With Glaucoma Vascular Changes in the I is and a Calcified Vascular G owth in the Left Occipital Lobe With Right Homonymous Hemianopia Arch Ophth 8 365-371 193_

[2813] Ellis R W B T igeminal Na vu and Hemangioma of M ninges Proc Roy Soc Med 25 1732 1734 1932

[2814] W ber F P and Harris K E A Cas of Widely Distributed Supe ficial T langiectatic Naevus Associated With Area of Na vu Anaemi u Indication That a Portion of the Cer bral Meninges are Similarly I volved Brit J Dermat 41 77 83 193

[2815] M irowsky E Halbs itig Na vu bei in m Epil ptike (S ktionsbe icht) Zt l 40 24

[2816] Touraine A and Nguye Van Vang État dysraphique famili l Bull Soc Franç d de mat et syph 43 1559-1561 1936

[2817] Greig D M Case of M ni geal Nae u Associated With Adenoma Sebaceum Edinburgh M J 28 105-111 19 ?

Chapter XXXIX

DISORDERS OF THE NERVOUS SYSTEM

Diseases of the Spinal Cord

Cord lesions may regardless of their nature produce *pigmentations* Such melanoses in the area of the skin supplied by the injured parts of the cord have been observed after gunshot injuries during the first world war Andre Thomas [818] found an increase of the pilomotor and sudomotor reflexes in the pigmented areas which suggests that the sympathetic system plays a part in the etiology of the pigmentations The pigmentations may appear after two weeks (Simons after E Kaufmann[11 5]) or after months or even years Sézary[18 8] feels that the slow appearance of the lesions makes a sympathetic etiology unlikely Since most of the cord injuries are fatal before the pigmentation has a chance to develop observations have remained rare Depigmentations of the skin after injuries or other lesions of the spinal cord e g tumors have occasionally been seen [11 5 166 663] In one case there was red dermographism above and white dermographism below the level of the injury

E Guttmann[2630] points out that the fibers conducting the sensations of touch and position ascend directly without crossing while the pathways for the *perception of warmth and pain enter a second neuron and* cross to the other side This explains the fact that a unilateral lesion of the spinal cord causes a contra lateral anesthesia for warmth and pain Localized destruction of the gray mat ter of the cord also causes abolition of the perception of warmth and pain with preservation of the senses of touch and position This dissociation can be seen in several localized cord lesions e g in syringomyelia hemorrhage into the gray matter and in intramedullary tumors The sensibility above and below the level of a circumscribed intramedullary lesion may be undisturbed if no direct fibers are involved Complete transverse lesions of the spinal cord leads to anes thesia below the level of the corresponding cutaneous innervation The lowest segments however often retain some sensibility

Status Dysraphicus —Status dysraphicus[2819 28 0] is a hereditary condition characterized by a great number of malformations The name is derived from the pathogenesis of the leading anomaly spina bifida caused by failure of the embryonal closing of the raphe of the medullary groove Funnel chest dispro portion between trunk and extremities abnormally long arms clubbed hands

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[28] André Thomas La pigmentation de la peau dans les blessures et les affections de la mo ll Rev neurol 28 102 10 19 1

[281] Bremer F W Untersuchungen zur Aetiologi der Syringomyelle Status dysraph cus Deutsche Ztschr f N rvenh. 95 1 19 6

[282] Breme F W Pathol anatom Begründung des Status dy aphi us D utsche Zt chr f Nervenh 99 104 1927

and clubbed feet polymastia asymmetry of the breasts and web formation are some of the stigmata Debility epilepsy psychoses acrocyanosis cataract hypogenitalism Horner s syndrome heterochromia of the iris and other disturbances may accumulate in one individual but more often such symptoms are grouped in families

Spina bifida occulta occurs in about 17 per cent of all persons a fact which has become known only with the advent of the x ray [81] Lumbar nevi and circumscribed sometimes excessive hypertrichosis over the spine may indicate the underlying cleft formation



Fig 356 T oph c ulcer aft r spinal o d tumo and op rati

Familial Trophedema —There also exists a relationship between status dysraphicus and the chronic *familial trophedema* of Nonne Milroy and Meige [82, 84] This is a hereditary condition which has been observed in as many as five generations [83, 85] though never in many members The disorder affects

[82] Curtiu F and Lorm I Klinische e biologisch u d rass hygi nisch Unt rsuchung n an 35 Fäll n tatu dy raphi u und i Fälten von 83 Ingomy II Ztsch f d ges N urol u I y hi t 149 1-4 1933

Le n Zur I inl ies T oph öd m M ig Mill oy D mat W hnsch 95 7 7 43 1937

J roscl y W C i m lsches Tropl öd m und Spina bifida occulta Beitra Helk 152 63 -611 1031

aint I M ig S y drom R adiol lin 2 045 0 5 1934

[83] M ig H Dy trophie oedémateuse héréditai Presse méd 2 341 189

[84] M ig H Compl m nt à l hi tori linique d un f mill att inte d trophoed m héréditaire R neurol 40 I 0 1 1933

the female sex more frequently than the male[25 4 25 7 25 9] The trouble is sometimes congenital but more often it starts later in life frequently in adolescence rarely later A slowly progressive later stationary edema develops in one or both legs rarely in the arms Painful febrile attacks have been observed to increase the edema [5 5 5 9] The fully developed lesion consists of an enormous firm edema The skin is smooth white or bluish or with a vascular pattern and feels cool Folds cannot be raised The contour of the legs is usually com

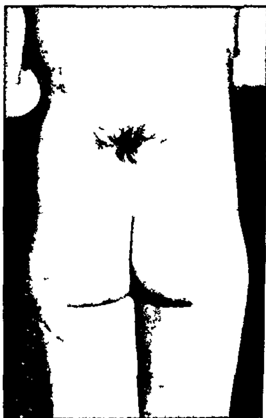


Fig 357 —Patch of hair over spina bifida

pletely lost A deep fold separates the leg from the foot The condition does not endanger life as shown by Meige s second report on the same case 35 years after his first presentation At the time of the second report the afflicted woman was 75 years old without other trouble than the edema

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[2827] Moniz E Sur l t opho dème chronique de Meige —Nouveaux cas —Considérations sur leur étiologie Rev n urol 28 1086 109 19 1

[2828] Tauber E Milroy s Di ease Arch Dermat & Syph 23 1127 1128 1931

[2829] McGuire J and Zeek P Pathogen sis of Ch onic Hereditary Edema of Extremities (Milroy s Disease) J A M A 98 870 873 193?

Besides status dysraphicus hypothyroidism[28, 2851] hyperthyroidism[28, 832] hypogenitalism,[28, 833] and melorheostosis Léri[28] have been found in association with the edema but *no definite etiology has been established* The dominant pathological feature is loss of the subepidermal elastica increase of collagenous fibers and widening of the lymphatic spaces *No effective therapy is known*



Fig 358 —*Spina bifida X ray of patient with patch of hair over lumbar spine*

Syringomyelia is much more closely related to status dysraphicus Curtius and Lorenz[821] found among 17 cases of syringomyelia 11 instances of spina bifida occulta In the families of patients afflicted with syringomyelia anomalies of the breasts and mental disorders are relatively common

Increase *of* neuroglia (gliosis) in the spinal cord and formation of tube like cavities within these lesions lead to a great variety of neurological symptoms

[28xx] M mmosh im A T ophoedema (M lg) Zbl 27 556 19 8

[x] P tráč k F Melke-Milroy sch Krankh it Česká d rmat 12 285 90 1931 Zbl 40 520

[x] [n] G l lschlag F I ber eine Kombination von Trophöd m M ige mit Melorheostose Léri Dermat W hnschr 89 1761 1766 19[x]

[x] Slatm n A F Ein Fall von Trophoed ma hro u um facl l in seinen Beziehungen zur Menstruation Zbl f Gynäk 51 22 9 19 7

varying with the sites within the central nervous system There occur sensory disturbances muscular atrophy beginning in the intermetacarpal muscles of the hands and ending up in characteristic contractions skeletal damage eye symptoms, and spasms The course of the disease is very slow the first symptoms usually remaining unrecognized over several years The patients rarely die of syringomyelia but they often succumb to intercurrent infections[2934] Recovery hardly ever occurs



Fig 3 9 —Nonne Meige Milroy disease Female aged 43 years Obesity mild pituitary symptom swelling of leg from childhood became worse at puberty Mother had the same trouble (Courtesy Wisconsin General Hospital)

Dermadromes —The dermadromes of syringomyelia are mainly due to the fundamental disturbance dissociated anesthesia While the perception of pain and temperature become lost the sense of touch and deep sensibility remain undisturbed Paresthesias are common in the early stages and the attempt to treat them with heat has often caused the first painless burns circulatory and possibly trophic influences may also play a part

[2934]Bing R and Haymaker W Nervous Diseases St Louis 1939 The C V Mosby Co

The patients hardly ever escape the traumatic and infectious complications In advanced cases the hands are rarely found free of crusty sometimes rhagadi form ulcerations of varying sizes often located on the extensor surfaces of the fingers Such trophic ulcers may lead to painless destructive lesions around the nails Mutilation resembling leprosy may ensue These fairly characteristic finger affections are called panaris analgésiques Transitory edema of the Quincke type[2630, 56, 2663] as well as lasting swellings represent another feature These swellings are often found on the hands giving them a succulent appear ance The edema may disappear and leave a flaccid atrophic skin with a silky or papyraceous surface or it may lead to a leathery uneven hypertrophy and hyperkeratosis unrelated to pressure or work (lizzard skin) The appearance of unusual keratoses on the hands should make the physician think of syringo myelia Regional [835] eruptions of large bullae in moderate numbers and unrelated to trauma may cause necrotic ulcerations [836, 837] another parallel to leprosy

The nails may become affected in many ways Hypertrophy and atrophy anomalies of position white color brittleness groove formation and complete loss have often been described [558, 838] The hair may gray early

The treatment is symptomatic Protection from trauma especially burns is most important

No skin manifestations were observed in 81 cases of amyotrophic lateral sclerosis [2839] though symmetric pigmentations of the forearms had been de scribed earlier (Bowing after E Kaufmann[11, 5])

Diseases of the Brain

A variety of dermadromes may be seen as results of cerebral lesions

Apoplexy may be followed by unilateral sweating of the paralyzed side (Binger and Berg after Marchionini [56, 663]) This has been called hémiplégie sudorale The galvanic skin reflex (Veraguth Tarchanoff s phenomenon) can not be elicited on the paralyzed side [2840]

Localized or unilateral swelling dryness and in about half of the cases scaliness occur Unilateral jaundice [841] occurs in *apoplexy* (See Chapter on Liver)

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[835] Schirne G Hyperkeratosis an der Handteller bei Überschreitung bei Syringomyelie Arch f Dermat u Syph **173** 27-33 1935

[836] Spillmann L Presentation d un malade atteint de gangrènes cutanées d origine syringo myélique Rev méd de l est **49** 260 1921 Zbl **2** 59

[837] Barney R F Syringomyelia Associated With Trophic Destructive Bulla Arch Dermat & Syph **33** 1094 1095 1936

[838] Frühwald Syringomyelie Zbl **45** 97

[2839] Wechsler J S Sapirstein M R and Stein A Primary and Symptomatic Amyotrophic Lateral Sclerosis (81 Cases) Am J M S **208** 70-81 1944

[2840] Essen K W and Lodesta H H Ablauf des galvanischen Hautreflexes bei halbseitigen Hirnläsionen Deutsch Ztschr Nervenh **138** 34-4 193

[841] Jag J H Ipsolateral Edema and Contralateral Jaundice Associated With Hemiplegia and Cardiac Decompensation Am J M S **177** 3 276 1929

Brain injuries may cause contralateral coating of the tongue [84] [813] alopecia [107] and sudden unilateral graying of the hair and beard (Gowers after J A M A [2844])

Wartenberg[2845] observed isolated pruritus of the nose in *tumors* of the temporal lobe He considered the itching and compulsory scratching of the nose which persisted in deep sleep as a valuable temporal lobe symptom but other neurologists[2834] deny its localizing value

Other occasional observations are unilateral seborrhea and sweating ecchymoses vitiligo and other pigmentary disorders of the skin [266] [663] (See also neurocutaneous diseases)



Fig 360 – Unilateral edema of the face on paralyzed side Three year after hemiplegia

Urticaria factitia[2846] is supposedly pronounced in idiopathic *epilepsy* but not in the jacksonian type During the epileptic fit the galvanic skin resistance is reduced [2847]

The epileptic seizure may be preceded by vasomotor symptoms like blushing or pallor The acute spasms of the respiratory muscles and the concomitant increased pressure in the vena cava may cause petechiae

These are often found in the conjunctivae and in the skin of the neck the chest and behind the ears [2834] The petechiae are rarely numerous (ecchymotic mask) [848] but they have some diagnostic or forensic value [849] Chloasma in the shape of the forehead ring occurs occasionally in epilepsy (See Encephalitis)

Börnstein W Trophisch Veränd ungen in d r Zungenschleimhaut (herdgekreuzt r Zung n belag) bei cort kalem Herd Z Neur **104** 776 799 1926

[84] Levinger E Unvoll tändiger Zungenb lag als vasomotori chtrophische Störung Deutsche med Wchnschr **52** I 707 708 19 6

[8 4] Vitamins and Human G ay Hair Editorial J A M A **122** 875 876 1943

[284] Wartenberg R Ein Schläfenlappensymptom Arch f P ychiat **103** 321 1935

[28 6] Camauër A F D agnostisch Wichtigk it de ödematösen oder urticariform n Dermographismus in der Neurologi Acta Conf lat Amer Neur etc **1** 98 110 19 9 Zbl **38** 189

[2 7] Porter J M Jr Galvanic Skin Phenomena in Epilept cs J Gen Psychol **11** 24-44 1934

[2848] De Blasi A Sulla co i detta maschera ecchimotica Ann ital di chir **13** 493 510 1934

[284] Milian G Piqueté purpuriq ie cervico tho acique des cri e comitiales Rev franç de dermat et de véné ól **4** 137 138 1928

Traumatization of the central nervous system may cause *purpura* of a distribution which is apparently governed by the nervous system Purpura up to the level of a spinal anesthesia [280] or generalized symmetric purpura after skull fracture [281] pertain here

Purpuric lesions have been described in many organic diseases of the central nervous system especially in multiple sclerosis [282]

Diffuse *hypertrichosis* has been observed in encephalitis following *complicated fractures* [283] in glioma of the temporal lobe [284] in disseminated sclerosis [285] and in several other lesions of the brain Hirsutism of this type may disappear with recovery

Encephalitis lethargica (Von Economo s disease) is an epidemic and contagious disease probably caused by a filterable virus After an incubation period of approximately a week the disease breaks out with mild fever and influenza resembling symptoms, often with icterus

Meningitic symptoms are lacking or mild but ocular palsies and headache develop frequently

In the course of a week sleepiness or irritability increases In the lethargic type the patient sleeps most of the daytime He can be aroused only with difficulty At night he is often restless In the irritable or hyperkinetic form the muscle tone is increased Tremor spastic paralysis fever and delirium are the main symptoms The acute stage may last several weeks or months The mortality of the cases with a stormy onset may be as high as 33 per cent

Another third of both types may recover completely and one third develops progressive or stationary sequelae among which Parkinsonism with paralysis agitans like symptoms rigidity salivation tremor is the most common one (Von Economo after Bing and Haymaker [334])

In young individuals change of character hypomania and psychoses may follow The pathological characteristics are inflammatory infiltrations and hemorrhages in the gray matter of the large nuclei and the frontal lobes

Dermadromes —Best known among a variety of skin manifestations of encephalitis lethargica is the profuse *seborrhea* [286] which has been found in from 35 [287] to 48 per cent (Stern after E Guttmann [530]) of the cases Rattner [288] found unusual oiliness of the face in only 8 per cent This symptom has rarely been seen in true paralysis agitans

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[280] Post F Purpura nach Lumbalanästhesie Klin Wchnschr 1931 II 2341 2342

[281] Kl dl r W Zur Frage d r Purpura traumatica München med Wchnschr 75 8 3 5 4 19 8

[282] Schindler R Nervensystem und Spontane Blutung n Berli 19 7 S Karger

[283] Caccialupuoti G B Sl iromi nc falltiche con r tropulsion catales la ed Ip rtri osi C rvello 10 113 1 6 1931

[284] Markoff N Hirsutism in Woman With Glioma of Left Lobe of Brain Schweiz m d Wchnschr 69 53-57 1930

[285] Le ing r F t be Entwicklu g o Hypertri hose b i w h r multipl Scl ro e Z Neur 122 499-509 19 9

[286] Cohn T Enc ph litis ohn Lethargi wäh end d r Grippeepid mi Zbl Neur 39 60 19 0

[287] W lman F B Seborrh ic D matitis i Post Epid mic E cephalitis Arch D rmat & Syph 21 690 1930

[288] Rattner H Changes in th Skin in Chronic Encephalitis Arch D rmat & Syph 31 35-37 1935

In typical cases the face appears as if it were covered with grease If the grease is wiped off it reappears within about 20 minutes Facial puffiness[2856] and complicating seborrheic dermatitis is not uncommon[2857] Seborrhea is comparable to other disorders of secretion like hyperhidrosis and excessive salivation and lacrimation which may cause chronic blepharitis and dermatitis of the lids The cause of the seborrhea is supposedly an inflammatory irritation of a center in the wall of the third ventricle[2859] Perutz[2860] could produce seborrhea in rabbits by stimulation of the interbrain

Trophic ulcers[2861] mostly in the nasolabial folds or around the nasal orifices sometimes invading the nasal septum and the upper lip have often been described[2862] The lesions may be very destructive and hard to cure



Fig 361



Fig 362

Figs 361 362 —Brown forehead ring in encephalitis lethargica (Courtesy Prof H Haxthausen Copenhagen)

These postencephalitic ulcers have in some instances been mistaken for rodent ulcers The sensitivity of pain and touch is preserved Analogous ulcerations in other areas e g the hands[2863] and the tongue (Schirmer and

[2859] Stiefler G (a) Seborrhoea faciei al ein Symptom der Encephalitis lethargica Z Neur 73 455 1921 (b) Seborrhoea faciei als isolierte postencephalitis he Veränderung Wien klin Wchnschr p 334 1924

[2860] Perutz A Lustig B and Klein A E Zur zentralen Regulierung des Fettstoffwechsels der Hautoberfläche Arch f Dermat u Syph 170 511 50 1934

[2861] Hoffman E Large Trophic Ulceration of Nose and Mouth Following Lethargic Encephalitis (Parkinsonism) Deutsche med Wchnsch 52 238 239 1926

[2862] Rosenberg S J and Solovay J Trophic Ulcer Following Encephalitis Lethargica Arch Dermat & Syph 39 85 89 1939

[2863] Michon P Troubles trophiques cutanés et parkinsoniens localisés Bull Soc franç de dermat et syph 38 1083 1084 1931

Baumann after Marchionini [66, 663]) are much rarer The localization in the naso labial folds suggests a connection with the seborrhea which is most active in this site

Chloasma [964] especially in the form of the brown forehead ring has been found repeatedly [858, 8] Such chloasmatic pigmentations are also known to occur in other intracranial processes e g epilepsy The typical brown forehead ring has the shape of a crossbow closely paralleling the hairline in the center and descending symmetrically toward both lateral ends of the eyebrows A nonpigmented zone separates the hair as well as the eyebrows from the lesions

Other reports on postencephalitic dermatoses include symmetrical gan grene [66, 663, 866] urticaria facticia Quincke s edema [2866] multiple paronychias (Schirmer after Marchionini [66, 663]) severe subungual hemorrhages [2867] diffuse alopecia resulting in almost total baldness in 4 cases [2868] bullous eruptions[2630] and Herpes Zoster [969] in 16 cases

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[2964] Haxthausen H Skin Changes Following Encephalitis Lethargica Acta dermat venereol **13** 408-416 1932

[2965] Anderson O and Wernoe T B Der braune Stirnring Ugeskr f laeger 1930 II 817 S 1 Zbl **36** 214

[2] Büchler P Vasomotorisch trophische Störungen bei Encephalitis epidemica Gyogyaszat **51** 718 1913 Zbl **12** 174

[2867] Von Poo F Hämatom des Nagelbetts bei post encephalitischem Parkinsonismus Dermat Wchnschr 1931 I 45

[2868] Stiefler G Zur Klinik der Encephalitis lethargica Wien klin Wchnschr **33** 286 289 1920

[286] Netter A 16 observations de zonas dans l encéphalite léthargique Zbl **36** 13

Chapter XL

PSYCHOSES AND PSYCHODERMATOSES

Psychoses

Kretschmer s[2870] work on physique and character correlated schizophrenia and the schizothymic personality with the asthenic and athletic builds and the circular psychoses with the pyknic type Though many of Kretschmer s affinities have been disputed [2871] the cutaneous dermadromes observed by him have to some extent been confirmed by his opponents [2872] This is particularly true of the *hair growth* in the main types of psychoses In the circular group a tendency toward hirsutism is striking These patients frequently have marked lanugo and axillary and pubic hair The men have a well developed beard growth of soft texture and equal distribution The hair often seems lighter during the stuporous period and becomes darker or reddish in the stage of excitation Such color changes were noticed as early as on the first day of the mental change [2873] In a 21 year old blonde woman the hair became partly white during several attacks of dementia praecox but it turned normal again when the spell ended [2877]

Male baldness seems to be more common among the circular than in the schizophrenic group and there is a difference in the character of the baldness The circular pyknic [2870] has pronounced temporo frontal calvities If he is bald the baldness is shiny and sharply bordered Kretschmer calls it a beautiful bald pate The baldness of the schizophrenic is usually less complete ill defined and irregular

There is a tendency to formation of folds in the scalp *Cutis verticis gyrata* and other acromegaloid traits have been found in schizophrenes by several observers [2874] [2875] The head hair of the asthenic or athletic schizophrene is often coarse in comparison with the soft hair of the pyknic circular On the forehead as well as on the nape of the neck the hairline is often straight and there is no temporo frontal notch Frequently it is lower so that a *fur cap* type of head hair results Bridges of hair from the head to the eyebrows and down to the lanugo of the back have been frequently found [2870] Junction of dense eyebrows (Synophris) occurs occasionally The terminal hair of the male schizophrenic is relatively weak though often coarse while the female schizophrenic has a tendency toward

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[2870] Kretschmer E Körperbau und Character ed ? Berlin 19? Julius Springer

[2871] Betz B J Somatology of the Schizophrenic Patient Human Biol **14** 19 234 194?

[2872] Iolle I I pc baustudien bei I v ho en Die männlichen Zirkulären Arch f Psychiat **17** 115 150 19 6

[2873] Eller J J Neurogenic and Psychogenic Disorders of Skin M J & Rec **129** 481 554 616 1929

[2874] Finkelstein B A Cutis verticis gyrata bei akromegaloiden Katatonen Monatschr f Psychiat u Neurol **105** 104 108 194

[28] Tomasino A Rara anomalia del cuoio capilluto rughe o pliche in un dement precoce Arch di antropol crim **55** 1008 1013 1935 Zbl **54** 104

hirsutism[2376] The latter observation is in contrast to Kretschmer However there is a general impression that some degree of hirsutism is found relatively often in various psychoses [877 879]

Alopecia totalis may occur in connection with depression [880] however the depression may also be of a reactive character due to the disfiguring loss of hair

Heller[558] was unable to confirm earlier claims of unexplainable and characteristic *nail* changes in psychoses *It is an old belief that the insane have* long or unusual nails, but this is not true * The transverse lines can usually



Fig 363 – Mental tardation Fur cap hair line (Court y Wisconsi G neral Ho pital)

be traced to intercurrent disorders Under proper care the nails of the inmates of asylums may be in better condition than the nails of the average population

Repeated loss of the nails and of the hair in circular psychosis has been described (Troisfontaines after Heller[558])

* The sam hou wa the thing fulfilled upon Nebuchadnezza and he was driven from men and did eat g as as oxen and hi body was wet wi h the dew of h aven till his hairs were grown like agl feathers and his n ils like birds claw – Dan I IV 33

[876] Mumford I B a d Ch v ns L C F An Investigation Into th Phy i al Characteristics of th kin in So n Types of I y hosi J M nt c 76 34 35? 193

[877] Elliott H F Comparison of Non psychotic Wom n With Schizophr nics With Respect to Body Type Sign of Auto omi Imbala ce and M n trual Hi tory I ychiatric Qu t 15 1 ? 1941

[878] Ep t in A L Somatologi al tudies in I ychiat y V u VI 7 N ur 183 5 6 588 5) 1933

[879] *Larbon C J Dallif C and Cav man Z Etu le anatomocli iqu ar u cas d vi ilism* pilaire Rev franç d en locri ol 2 17 185 19 711 19 497

[880] Allen C and Carlyle-Gall L D pression Hypose ual Alopecia Syn lrome Brit M J 2 ? -68 194?

The observations on the status of the skin in the insane have not yielded many tangible results Vascular symptoms are first on the list Kretschmer[870] also Mumford and Chevens[86] emphasize the rosy complexion of the circular pyknic in comparison with the pale asthenic schizophrenes

The *vasomotor* lability of the pyknic also expresses itself in a greater tendency to blushing and rosacea Some authors found the skin of the circular in good condition rather moist with a well developed panniculus adiposus The skin *of the schizophrene is usually paler flaccid and unhealthy Acne is frequent*[85] Dryness and a *keratotic* tendency has often been considered a characteristic of the skin of the insane[851] Mumford and Chevens[86] relate this symptom to the schizophrenic



Fig 364 —Mental debility Female aged 4 years Hypertrichosis

The most important vascular phenomenon of the schizophrene is *acrocyanosis* This has been confirmed by many writers[86, 88, 2883] Closely related to the acrocyanotic syndrome is the pseudo edema of the insane (Dide Trepsat Kraepelin after Simon[2883]) In acrocyanosis the *acra* are bluish with red vascular patterns cold slightly swollen but not pitting The swelling may reach up to the knees and a fold may be marked at the ankles and at the base of the toes There is prolonged white dermographism with red borders lasting from one and a half to two hours

Red dermographism is common in a great variety of psychoses[884]

Generalized addisonoid *melanoderma* in catatonic schizophrenia has been observed in several instances[885]

Spontaneous and unexplained bullae with subsequent ulcerations occur even in bedridden patients without undue exposure to traumatism In the *mentally deficient* anomalies of the hair pigmentation acrocyanosis pseudo

[851] Goldbladt H and Bermann S Sur les recherches de la peau chez les aliénés Schweiz Arch f Neurol & Psychiat **19** 234 41 1926

[88] Stern E S Etiology and Pathology of Acrocyanosis Brit J Dermat & Syph **49** 100 108 1937

[2883] Simon C Dermatoses en rapport avec des troubles du système nerveux Nouvelle pratique dermatologique vol 5 Paris 1936 Masson & Cie pp 749 867

[884] Petronelli F Il dermografismo nelle psicopatie h C vello **11** 40-46 1932 Zbl **42** 83

[885] Wigert V Katatonie und Melanodermie Acta psychiat (Kopenhagen) **1** 84 144 1926 Zbl **22** *218*

edema malformations nevi hemihypertrophy [2886] and scars from biting the hands and wrists [887] have frequently been recorded but the statistics are controversial and [976] [888] some lack sufficient controls Mumford and Chevens [8 6] emphasize the juvenile character of the skin in mentally retarded adults

The dryness of the skin and hair the tendency to eczematous eruptions the large protruding tongue malformations of the ears epicanthus and mongol spots [889] are the well known external signs of *mongoloid idiotism* Familial xeroderma pigmentosum may be associated with severe retardation [890]

Psychogenic Dermatoses

A great number of *cutaneous reactions to psychic stimuli* are known One has to assume that the autonomic system mediates the psychic impulses to the effector organs in the skin by the liberation of acetylcholin or sympathin (See autonomic system) Pallor blushing perspiration gooseflesh and the graying of the hair are proverbial phenomena caused by fear shame rage embarrassment excitement worry and other psychic factors Certain sensations in the skin like spine tingling shuddering itching and hair raising may also be produced by merely psychic causes e g reading an exciting story fear acoustic stimuli as sour notes and shrill sounds or the touching of certain materials like silk cardboard and rough wood Using laboratory methods very ensitive responses can be demonstrated Not only actual sensations but even the mere imagination of a sensation like pain reduces the electric resistance of the skin in a typical way which is demonstrable by Tarchanoff s psycho galvanic reflex This accurately measurable drop in electrical resistance is due to the sympathetic stimulation of the sweat glands [631]

The skin temperature depends on the arterial tonus which responds readily to psychic stimuli A local temperature increase of 0 2 centigrade can be caused by mental concentration on a spot [2891] The famous lie-detector is based on such psychogenic reactions in the skin and other organs It is not difficult to conceive that inflammatory processes which are so intimately related to vasodilation may in some instances be produced by psychic causes Many experiments have proved the truth of this assumption There are many clinical observations which support the *psychogenic* etiology *of some dermatoses* but it is more often true that psychic stimuli enhance or impair an existing dermatosis than that they actually cause it The experimental methods do not try to explain the psychic part of the sequence emotion—somatic changes They concentrate on the latter part The greatest attempt, not to explain or to locate the psyche

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[2886] Wak fi ld F G Co g ital Hype trophy of Left Should Girdl A m a I Hand With Nevu a i I V leos V ins Am J M 8 171 569-5 5 19 6

[887] Butterwo th Th n I Wilso M Jr Incil e of Di ases of th Skin in Feeble minded P rson Arch D mat & Syph 38 203 209 1938

[888] Burk N H M Stigmata of Deg n rati n in Relation to Mental D fi i y Proc Roy Soc Med 24 413-4 8 1931

[889] Bru hfield T Mo golism Brit J Child Dis 21 211 258 19 4

[890] De Sa tis C d Cacchion A I Ill zia erod rmica, Riv sper di f nlat 56 269-292 193 Zbl 43 418

[2891] Berger H Psy hisch Beei flussung d r Hautt mperatu Journ f P ychol u N urol. 27 209-2 1 1922

but to permit a glimpse of its mechanisms has been made by Freud and his psychoanalytic school

According to this doctrine the powerful source of psychic energy the mystic Id makes contact with somatic processes somewhere in the form of instincts A resistance is set up against the demands of the instincts (Freud after Hinsie and Shatzky[2889]) This leads to conflicts because the suppressed or repressed instincts are not deprived of their power They continue to seek discharge comparable to potential energy which tends to transform itself into kinetic energy Somatic processes including disease may be one of the forms of transformation In this way conflicts may lead to disease The term psychodermatosis* seems appropriate for dermatoses of psychogenic origin

The case material illustrating the psychogenesis of dermatoses is large but not always conclusive Small numbers the fluctuating course of the dermatosis in question, and accompanying dermatological treatment often obscure the evidence which is supposed to prove psychogenesis But in spite of these limitations the existence of psychogenous dermatoses and the value of psychotherapy cannot be denied [2891 2893 2903]

Vascular Phenomena —Psychogenic *erythema* as an expression of modesty embarrassment or excitement is usually restricted to the face and neck About the neck or upper chest it may assume a blotchy pattern especially in women who generally are much more likely to blush than men Children of both sexes seem to blush equally with various emotions especially with guilt on telling a lie Emotional erythema has been seen in atypical sites to which the mind of the patient had been concentrated A patient blushed emotionally around a tuberculous sinus of long standing[2893] A woman who is examined gynecologically for the first time may show emotional erythema on her abdomen[2893 2895 2898]

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* The word neurodermatosis should be restricted to the dermadromes of organic diseases of the nervous system The word neurosis is often being used for a relatively minor disorder of the psychic constitution which is not a psychosis

[2889] Hinsie L E and Shatzky J Psychiatric Dictionary New York 1940 Oxford University Press

[2893] Sack W T Psych und Haut Handb d H u Gk 4 ? 130 149 1933

[2894] Gillespie R D Psychological Aspects of Skin Diseases Brit J Dermat **50** 1 16 1938

[2895] Mayr J K Uber Psychogenese von Hautkrankheiten Zbl **23** 1 ?

[2896] Klaude J A Psychogenic Aspects of Diseases of the Skin Arch Dermat & Syph **30** 881 883 1934

[2897] MacKee G M Neurotic Excoriations Arch Dermat & Syph **1** 256 19 0

[2898] Weber J Die neurotischen und hysterischen Dermatosen Dermat Wchnschr 1933 I 461–470 513 518

[2899] Pusey W A and Senear F E Excoriations Cases Arch Dermat & Syph **1** ? 0 19?0

[2900] Michelson H E The Motivation of Self Induced Eruptions Arch Dermat & Syph **51** 245-2 0 1945

[2901] Obermayer M E Functional Factors in Common Dermatoses J A M A **122** 86? 1943

[2902] Lynch F W Hinckley R G and Gowan D W Psychobiologic Studies of Patients With Atopic Eczema Arch Dermat & Syph **51** 251 60 1945

[2903] van de Erve J M and Becker S W Functional Studies in Patients With Neurodermatoses J A M A **105** 1098 1935

Blushing and fear of embarrassing blushing can sometimes be traced to early sexual emotions The psychoanalysts found an underlying Oedipus complex in some pronounced cases [894]

Psychogenic *hemorrhages* may be caused by a gruesome sight [895] or similar experiences Schindler [8] who has devoted a monograph to the subject of spontaneous neurogenic and psychogenic hemorrhages saw the purpuric spots most often on the lower legs of hysterical persons

He describes three cases which were cured by hypnosis or psychotherapy The purpuric lesions could be provoked by hypnotic suggestion [2904] Kohnstamm could inhibit bleeding from needle pricks by the hypnotic suggestion that the pricked left index finger would not bleed The pricked index finger of the right hand for which normal conditions had been suggested bled in the usual manner [2648]

Mystic Stigmatization —In this connection the phenomenon of *stigmatization* has to be mentioned The term is derived from the sixth chapter of the Epistle to the Galatians in which the Apostle Paulus says I wear the mark (stigmata) of the wounds of Jesus on my body [85 2905 907] Thus it means the appearance of skin lesions resembling the wounds suffered by Jesus during the crucifixion

The numbers of more or less well acknowledged cases vary from 80 to 321 according to various Catholic sources [905] The Catholic church has at least in modern times exercised great skepticism in this matter The most famous and if Saint Paul s word is not taken literally probably the first of the stigmatized was Saint Francis Sixty two have been beatified or canonized A medical report of an eighteenth century ca e of stigmatization including autopsy has recently been made accessible [2912] Twenty nine cases occurred in the nineteenth century and at least three have been observed by trained modern scientists The last case was that of the still living Theresa Neumann of Konnersreuth in the Bavarian Palatinate The case probably resembled earlier observations in many respects [906 2907] Ewald [908] professor of psychiatry at the University of Erlangen who observed Theresa and furnished a now famous expert opinion for the physician of the bishop of Regensburg saw nickel sized dry scab covered hemorrhagic and tender lesions on the dorsa of the hands and feet The scabs developed from blood which oozed through the thin epidermal membrane during the ectasies There were smaller lesions on the corresponding spots of the palms and soles and over the heart next to the sternum The latter the so called chest wound had a slightly raised edematous appearance

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[2904] Werth r J A Symposium on Psychog nic Dermatoses Dermat Wchnschr 94 70 1932

[2905] Jak bi W Die Stigmatisierten B it äge zur Psychologi der My tik Gr nzfragen d Nerv n u Seel nlebens No 114 pp 1 57 Münche 19 3 J F Bergmann.

[2906] Schult J H Stigmatization Deutsche med Wchnschr 53 1544 1556 1927

[907] Simon C Les Stigmates cutanées des mystiques Bull méd Paris 47 667-671 1933

[908] Ewald G Die Stigmatisi rte von Konnersreuth Untersuchungsberi ht und gutachtliche Stellungnahme München. med. Wchnschr 74 1981 1992 1927

The American dermatologist Klauder,[2909] who examined Theresa nine years after Ewald[2908] found a remarkably square dry glazed hemorrhagic lesion without any inflammation ulceration or destruction The clot seemed in the skin rather than on it Klauder[2909] also saw sharply outlined pear shaped congestive areas 0 5 cm long on the forehead These stigmata which symbolized the wounds from the crown of thorns did not have crusts



Fig 365 —St Francis receiving the stigmata (Painting by Francisco de Zurbaran With permission of the Musée du Louvre Paris)

On Friday Theresa went into a state of ecstasy in which she seemed to endure or witness the crucifixion of Christ During her ecstasy the stigmata became redder The marks did not heal in the interval In the scant secretion of the thoracic stigma and in the tears blood was found microscopically According to reports which Ewald could not verify and the objective truth of which he could not believe Theresa did not eat more than a quarter host with 3 c c of water daily There were no stools but small quantities of urine containing

2909 Klauder J V Stigmatization Arch Dermat & Syph 37 650-6 9 1938

acetone were secreted The girl lost nine pounds during the ecstasy but regained her weight during the interval in spite of doing house work and other activities Ewald and other medical observers[2909] arrived at the opinion that Theresa s stigmata were genuine and not artificially produced

The psychiatric diagnosis made not only from the ecstasies but from many other preceding manifestations was severe hysteria

Allergic Phenomena —Purely psychogenic *urticaria* is rare [648 2910 2911] Psychic factors however were noticeable in 18 per cent of 170 cases [913] of urticaria and angioneurotic edema Stokes Kulchar and Pillsbury [914] in a thorough study of 100 cases estimate that psychogenous influences are the sole cause of urticaria in 12 per cent and a contributory cause in 68 per cent The urticariogenic psychogenous background seems to lie in a personality type, rather than in external impinging circumstances [901 2915, 916] Allergic urticaria may result in a conditioned reflex and persist long after the exposure to the excitement has ceased [159 917] Hebra described the case of a woman who developed urticaria by the mere thought of some urticariogenic substances (Veidsen in discussion to Kohnstamm and Pinner [918])

In a well observed case [919] of suspected allergy to quinine urticaria could be produced by hypnotic suggestion of taking quinine and quinine could be taken in hypnosis without producing urticaria if it was suggested that it was not quinine Kohnstamm[2970] performed the following experiment in the presence of a group of neurologists A cross was drawn with a pencil on both arms of a subject under hypnosis The suggestion was given that on the left side an urticarial wheal would develop within two hours whereas the right side would remain unaltered After about an hour under supervision the wheal formation on the left side began Urticaria factitia was excluded

Some patients develop urticaria on excitement Some are able to produce wheals in a certain spot by mental concentration on this area [2895 898] Urticaria after coitus probably belongs to this group [29 1 9] Dermographism is supposed to be common in neurotic patients [2896] The cholinergic character of emotional urticaria has been thoroughly investigated Rothman [6 4] considers this condition

[1] Drake J A Urtica ia Evoked by Emotion Brit J Dermat 43 184 185 1931

[911] Dunbar H F Phy ical and Mental Relatio ship in Illness Am J Psychiat 91 541 56 1934

[2] [1] Jarcho S Zambeccari Life of Maria Cate ina Bro di Bull Hist Me i 15 403-419 1944

[913] Fink A I and Gay L N Review of 170 Cases of Urti a ia and Angion uroti Edema J Allergy 5 615 1934 al o Bull John Hopkins Hosp 55 280 29 1934

[9] Stokes J H Kutchar G A and Pillsbu y D M Effect on the Skin of Emotional and Nervous States (Urticaria) A ch De m t & Syph 31 470-499 193

[915] Stokes J H The Personality Facto in Psychon uroge ous Reactions of the Skin Arch Dermat & Syph 42 780-801 1940

[916] Bierman W Treatment in Periph ral Vascular Disea Arch Phys Therapy 21 267 69 1940

[917] Sack W Zum Mechanismus d r psychophysisch n Schaltung Nerv narzt 6 57-6 1933

[918] Koh stamm O a d Pi n r M Blasenbildung durch hypnotische Suggestion Arch. f Dermat u Syph 91 3 9-380 1908

[9] Kartamisch w A J Ueber d Wesen d r psychisch n U ticaria Arch. f Dermat. u Syph 173 531-536 1936

[2970] Kohnstamm O Demon tration Deutsch Ztsch f Nerv h 43 447-448 1911 191

[2971] Hirschfeld M Sexualpathologi v l 1 Bonn 19 A Marcus and E Weber p 58

[2972] Wengraf F Fine De matose post coitum Psychoth r Prax 1 50-5 1934

as one of the rare cases of allergy to a physiological metabolic product namely acetylcholin Rothman[2654] has in two out of three cases successfully desensitized patients with emotional urticaria by gradually increasing intradermal doses of acetylcholin

Many allergic phenomena like urticaria asthma and hay fever are highly subject to psychic influence There is much evidence accumulated that certain types of character namely the driving high strung subtle intelligent ambitious sensitive also the imbalanced and maladjusted predispose to allergy[2928] Worry grief anxiety, fatigue stress and strains unsatisfied longing for love and affection may increase specific allergic reactions and prevent their healing[159] Experimental allergic wheals in persons with pronounced allergy can be increased or inhibited by hypnotic suggestions[2924, 2925]

Other Psychogenic Dermadromes—*Sweating*—Mental stimuli e g mental efforts in solving an arithmetical problem pain or excitement may in some persons evoke sudden frontal axillary and especially palmar sweating[2894, 2923, 2926, 2927] Apprehension of having a wet hand when shaking hands may cause palmar perspiration

The sweat secretion generally but especially that of the palms and soles is a sensitive somatic receptor of psychic stimuli[2927] This is best demonstrated by Tarchanoff s psychogalvanic reflex (see above) which indicates increased perspiration by lowered electric resistance of the skin The shouting of words to the test person is sufficient to evoke the reflex *Dyshidrosis* is in some cases quite subject to psychogenic factors

Psychogenic blisters represent a more severe reaction than the changes which have been mentioned so far The blisters may even be followed by necrosis While great skepticism prevails with regard to the so called pemphigus hystericus of the older authors[2928] it cannot be doubted that bullae can be produced by hypnotic suggestion of a burn[2893, 2895, 2918, 2929] Kreibich and Doswald[2929] hypnotized a physician and touched him with a stick of wood suggesting that he was being burnt with a match After three minutes an erythema the size of a match head appeared and after three more minutes a blister of the same size was visible Biopsy after 24 hours revealed changes identical with that of a third degree burn[289]

Similar experiments have been repeated by many authors and with precautions which ought to rule out fakery including a plaster of Paris dressing during the experiment

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[2923] Stokes J H and Beerman H Psychosomatic Correlations in Allergic Conditions Problems and Literature Psychosom Med 2 438-458 1940

[2924] Diehl F and Heinichen W Psychische Beeinflussung allergischer Reaktionen München med Wchnschr 78 1008-1009 1931

[2925] Marcus H and Sahlgren E Untersuchungen über die Einwirkung der hypnotischen Suggestion auf die Funktion des vegetativen Systems Acta psychiat et neurol 11 119-126 1936

[2926] Kuno Y Physiology of Human Perspiration London 1934 J & A Churchill Ltd

[2927] Kosaka T Demonstration of Psychical Sweating by Means of Minor s Method Jap J med Sci Trans III Biophysics 2 2 1931 Zbl 42 303

[2928] Cascella F Ipoevolutismi e infantilismi universali nelle insufficienze psichiche Rassegna di studii psichiat 19 421-465 1930

[2929] Kreibich K and Doswald D C Posthypnotische Hautphänomene Monatsh f prakt Dermat 43 634-640 1906

Herpes simplex and especially herpes genitalis is subject to psychogenic influences such as guilt and fear of venereal infection after extramatrimonial coitus.

Pruritus is highly susceptible to psychogenic influences.[993] Every dermatologist knows of patients with lichen ruber and lichen Vidal, chronic eczema, psoriasis and prurigo whose skin disease is more itchy on excitement and calms down when the patient does. However, while mental impulses are very common contributory factors, purely psychogenic pruritus is rare.[1116, 930]

In order to prove the existence of completely psychogenic pruritus, Sack induced pruritus by hypnotic suggestion in the locally anesthetized finger of a patient. Pruritus may be a symptom in endogenous and reactive depressions.

The sexual background of anal and vulvar pruritus has frequently been analyzed.[894, 29 3] Many psychoanalysts believe that the pruritic seizures and the relief of tension achieved by violent scratching are sexual or homosexual equivalents. These relations seem to have been overemphasized.[931]

Psychogenic eczema is illustrated by the following case.[293] Psychoanalysis traced the origin of an eczema on the buttocks to a nauseating dream in which the patient had seen himself covered with feces as high as the eczema indicated. Psychoanalysis cured the patient.[923, 2933]

Sudden *blanching of the hair* caused by terrifying experiences is still controversial. The two leading American textbooks of dermatology arrive at opposite opinions. Ormsby and Montgomery[633] admit it as a rare probability of clinical experience, while Sutton and Sutton[667] explain it as the result of the removal of cosmetic coloration or of the application of a bleach. The main argument against it is the lack of greater numbers of observation in both World Wars with millions of terrifying occasions. The number of well documented cases[934] seems too small to rule out the possible errors, especially that of having been gray before the event.[2931] The physiological possibility of a sudden graying must be admitted. Landois's old theory that in such cases the pigment is hidden by reflecting gas bubbles has found considerable supporting evidence.[2844]

Mental stress, strain and shock probably play an important role as a trigger factor in *alopecia areata*.[293]

In the opinion of the *psychoanalysts* psychogenic dermatoses always have a meaning.[2936] In some instances they symbolize their origin as in the case of ecchymoses after seeing blood[2890] in the mystic stigmas or in the cases of psoriasis provoked by the terrifying and prolonged sight of decomposing corpses in

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[2930] Pearson, G. H. J.: Some Psychological Aspects of Inflammatory Skin Lesions. Psychosomat. Med. 2: 22-33, 1940.

[2931] Klauder, J. V.: Psychogenic Aspects of Skin Diseases. J. Nerv. Dis. 84: 249-273, 1936.
Bretschneider, A.: Psychogene (on iroge e) Krankheitsbilder. Arch. f. Kinderh. 98: 51-55, 1933.

[2932] Rogerson, G. H.: Psychological Factors in Skin Diseases. Practitioner 142: 17-35, 1939.

[2933] Vigolo-Lutati, G.: Canizie precoce e psicopatie di guerra. Policlinico (sez. prat.) 25: 680, 1918.

[2935] Ingram, J. T.: Baldness, Causes and Treatment. M. Press 209: 41-44, 1943.

[2936] Schilder, P.: Psychophysiology of the Skin. Arch. Dermat. & Syph. 30: 853-856, 1934.

front of trenches where the patient fought [937, 1938] In some of these cases cure has been accomplished by hypnotic suggestion Schilder [938] expresses the opinion without proving it that anal itching is an expression of sadomasochistic tendencies blushing manifests a narcistic attitude and blisters and hemorrhages are closely related to a hysteriform attitude with a strong infantile Oedipus complex

While classic psychoanalysis has found but little acclaim among the dermatologists, the importance of tensions conflicts emotions overwork fatigue shock worries insomnia inferiorities frustrations and other psychic factors on the origin and course of dermatoses has been emphasized time and again

This has been done in the most human practical and convincing way by Stokes [1939] Purely psychogenic dermatoses are rare and do not develop typical morphological pictures with the exception of the self inflicted dermatoses

Yet it is exceedingly common that the psyche influences the course of a disease for better or worse psoriasis lichen planus [1940] chronic eczema lichen Vidal dermatitis herpetiformis and alopecia areata furnish the best examples (see also Obermeyer[1901]) The psychosomatic relationship of *atopic dermatitis* is particularly striking [1931] These patients are often highly intelligent aggressive and ambitious as well as tense and fidgety It is more likely that their nervousness is primary rather than due to their itching and disfigurement which of course may also leave its mark Their behaviour and character are quite different from other suffering or disfigured people Family conflicts are often in the background of such cases not infrequently caused by arguments on the treatment or diet This was strikingly illustrated in one of the author s cases An intelligent boy of 13 with severe atopic eczema improved immediately after the mother was advised to discontinue all discussions and arguments on his diet which had disturbed almost every meal Later the trouble recurred on other conflicts Overattention as an only child or resentment because of sibling rivalry, frustration and parental rejection may also occasionally express themselves in more intensive itching and scratching and consequent impairment The children soon learn to use their ailment as a weapon [43, 1941]

In this group probably belongs *acne urticata* [294] In this condition the lesions which may occur on the face or anywhere on the body are at first wheals or papules which itch intensely and become infiltrated and excoriated under constant scratching They disappear after several weeks leaving a pigmented spot The eruptions may keep appearing for years In some of these cases a psychogenic background is obvious In one of the author s cases the disease broke out in a young woman after the husband had gone overseas and eased up on the news

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[937] Bunnemann O Psychogenese von Hautsymptomen Ztschr f d ges Neurol u Psychiat 88 589-600 19 4

[1938] Bunnemann O Ueber psychogene Hautveränderungen Psychotherapeut Prax 1 3 -36 1934

[1939] Stokes J H Functional Neuroses as Complications of Organic Diseases An Office Technic Approach With Special Reference to the Neurodermatoses J A M A 105 1007 1013 1935

[294] Goeckerman W H The Relationship of Emotions and Cutaneous Lesions Med Clin North America 14 645 64 1930

[1941] Rogerson C H Psychotherapy and the Asthma Eczema—Prurigo Complex in Children Brit J Dermat 46 368 3 8 1934

[1942] Kaposi M Ueber einige ungewohnliche Formen von Acne (Folliculitis) Arch f Dermat u Syph 26 87 96 1894

that he was out of the danger zone The patient was an *intelligent high strung* person of a type commonly encountered in atopic dermatitis to which the condition seems to be related Acne urticata also may be seen in atopic dermatitis

Burning tongue is highly susceptible to psychic influence In this condition the impulse may act through the sensitive psychosomatic mechanism of the gastric acidity Becker and Obermayer [943] call *neuronychia* nail changes which either consist of separation of the nail from the bed or of superficial pitting thickening thinning or splitting The authors saw the condition associated with neurodermatitis or as the only somatic manifestation of nervous instability and exhaustion

Hysteria —Conscious or subconscious production of symptoms the main feature of hysteria leads into the field of the self inflicted dermatoses (neurotic excoriations dermatitis factitia) The variations of clinical appearance are innumerable but there are some features which are often encountered The feigned



Fig 366 — Acné ex orlè The scali ess is caused by ultraviolet light

lesions are usually within the reach of hands preferably of the right hand The artefacts and their scars often have a strange angular round or linear unnatural appearance which arouses the suspicion of the experienced dermatologist [2944] Sometimes traces of a chemical u ed in the production of lesions can be found in the surroundings or on the scab If the circumstances permit the application of a sealed occlusive dressing especially with plaster of Paris is advisable If healing of the suspected lesions of long standing follows further evidence of self infliction is given

[943] Becker S W a d Obermayer M E Mod rn D rmatology and Syphilology Philad lphia 1943 J B Lippincott Co

[944] Senear F E and Shellow H Neurotic Excoriations Arch. Dermat & Syph. 46 8 4-825 1942

However one should keep in mind that the typical pathomimic changes represent only a minority among the great variety of entirely or partially self inflicted lesions More commonly a spontaneous dermatosis like acne or a patch of eczema is kept going by picking scratching or treating Excoriated acne is found not only in young girls (Brocq s acné excoriée des jeunes filles) but also in middle aged women

The psychology of self induced eruptions [853, 2894, 897, 900, 2933] ranges from the sometimes criminal, but simple and mentally normal cases of military or civilian malingering to more complicated and often decidedly pathological states of mind In one of these cases (Dieulafoy after Simon[2583]) recurrent deep ulcerations of the hands and arms led to various major operations and finally to the *amputation of one arm The patient would not have hesitated to have his other* arm amputated if the right diagnosis had not been made Under some grilling the patient admitted that he had placed pieces of potassium hydroxide on the



Fig 367 Trichotillomania

mantlepiece and then put his arm on it Similar cases are on record The most *plausible motivation is an escape into disease The suffering arouses sympathy* and attention which the patient is craving Strangely enough the motivation may also be lack of erotic attention A woman may try to get the sympathy and with it the love of her husband This might be called the 'poor little dear motivation Psychoanalysis may also detect underlying unconscious motives



Fig 368 —Trichotillomania

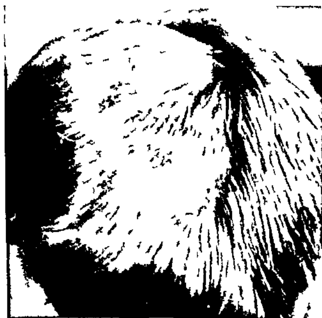


Fig 369 —Tri hotilloma ia. (Courtesy Divisi n of D rmatology D partme t of Medicin Uni sity of Chicago)

of guilt and punishment[2900, 2945] In this group belong the patients who keep pyodermic lesions on the face open with tweezers

Some of these patients are *feebleminded* who without any purpose follow an exaggerated urge to remove all little follicular plugs to dig after or pull out ingrown hairs and to scratch every scale on the scalp

The cases of neurotic excoriations lead to the true cutaneous *manias and phobias* There is the urge to rub the hair between the fingers to bite the nails to break hairs or to pull the hair out (trichotillomania) This latter condition



Fig 370 —Neurotic excoriations

usually found in children is often combined with anomalies like enuresis and mental retardation[2946, 2947] paranoia[2948] or postencephalitic state[2949] It has also been observed as a psychic epidemic in institutions (Haldin Davis in discussion to O Donovan[2950]) Transitory cases without apparent deeper significance are also known[2951] Apparently unique is a case of plucking the mustache[2952]

[2945] Casazza R Sull importanza di fattori p ichici in dermatologia (a proposito di autolesioni cutanee in I teriche) Boll d Soc m d-chir Pavia **44** 115 16? 1930 Zbl **35** 261

[2946] Dohi S Ueber Trichotillomanie Dermat Ztschr **58** 236 239 1930

[2947] Tarozzi G L Su di un caso di Trichotillomania Pediatria prat **10** 393-407 1933

[2948] Chashi K Ein Fall von Tri hotillomania Jap J Dermat **32** 70 193. Zbl **42** 61?

[2949] Perantoni Satta G Considerazioni cliniche su un caso di pseudotricotillomania Dermosifilografo **6** 449 460 1931

[2950] O Donovan W J Infantile Trichotillomania Proc Roy Soc Med **26** 836-838 1933

[2951] Bleyer A Hair Plucking Am J Dis Child **51** 336-337 1936

[2952] Photinos I B Aetiologie der Trichotillomanie Dermat Ztschr **61** 239 240 1931

Cutaneous phobias and *hypochondriac complaints* which appear suddenly should be reason to search for an underlying psychosis [873, 2953] or addiction to morphine or cocaine

Patients who persistently bring little follicular plugs scales or woolen fibers wrapped in paper or kept in a box to convince the doctor that they have worms or insects in their skin that they feel them creeping clicking digging and that they have to crush them between their fingers have delusions and belong to a psychiatrist [2954, 2956] Such delusions of parasites or dermatozoa may occur in the toxic psychoses in dementia praecox in involutional melancholia and in paranoia and paranoid conditions The prognosis is poor Only about 10 per cent of the reported 51 cases have been cured [2955] A greater significance may be attached to the severe cases of patients who wash their hands excessively avoid touching a door handle and have constant fear of body odor or of being dirty or of blushing



Fig 371 —Neurotic nail biting

Tattooing while normally a badge of membership to certain groups (sailors) *or just being a fad may also express psychopathological conditions* [2957, 2958] *with* an erotic homosexual or criminal background During the second World War the rejection rate for tattooed men was almost 50 per cent greater than for nontattooed men and 58 per cent of all rejections among tattooed men were on the basis of neuropsychiatric disability in contrast to only 38 per cent among the nontattooed [2959] These military statistics are according to the authors

[2953] Graham Little E Neurotic Excoriation Proc Roy Soc Med 24 686 1931

[2954] Ekbom K A Praeseniler Dermatozoenwahn Acta psychiat et neurol 13 227-259 1938

[2955] Wilson J W and Miller H E Delusion of Parasitosis (Acarophobia) Arch Dermat & Syph 54 39 57 1946

[2956] Wright G S Psychosomatic Aspects of Dermatoses Clinics III 711 727 1944

[2957] Bromberg W Psychologic Motives in Tattooing Arch Dermat & Syph 30 888 892 1934

[2958] Parry A Tattoo New York 1933 Simon & Schuster Inc

[2959] Lander J and Kohn H M Tattooing Among Selectees (Psychiatric Significance) Am J Psychiat 100 326-327 1943

based on numbers large enough to be valid though exact absolute figures are not given Among the men rejected for antisocial inclinations 68 per cent had multiple tattoos

Psychotherapy of Dermatoses — If a psychic factor causes or as it more frequently happens influences the course of a skin disease, the removal of this cause should be tried The office technique approach [901, 939] may be learned depending on the interest and aptitude of the dermatologist but at the present stage of our training the aid of a trained psychiatrist should be sought [2941, 960] to the greater advantage of both parties

Hypnosis has occasionally been successful in the treatment of psoriasis [961] and eczema [296]

The *psychotherapy of juvenile as well as ordinary warts* has been practiced by lay healers for centuries under many forms [963] Bloch [964] stimulated scientific interest in the matter by healing 44 per cent of verrucae vulgares and 88 per cent of verrucae planae by verbal suggestion painting with color and turning on a buzzing electric motor No consensus exists about the post hoc ergo propter hoc but it is the impression of many experienced dermatologists that suggestion therapy is effective in a varying percentage Some cases are very impressive [2963, 2965] Memmesheimer and Eisenlohr [966] treated 70 out of 140 cases of ordinary warts by suggestion and left the other 70 untreated There was no significant difference in the percentage of cures The cure of condylomata acuminata by suggestion has been reported by Bonjour [2967]

2960 Weiss E and English O S Psychosomatic Medicine Philadelphia 1943 W B Saunders Co

2961 Wisch J M Anwendung der Hypnose bei Psoriasis Dermat Wchnschr 100 231 236 1935

2962 Dubnikov E Zur Frage der Behandlung des Ekzems nervösen Ursprunges durch Hypnotismus Vrach delo 15 634-636 1932 Zbl 45 4 0

2963 Zwick K G Hygiogenesis of Warts Disappearing Without Topical Medication Arch Dermat & Syph 25 508 521 1932

2964 Bloch B Ueber die Heilung der Warzen durch Suggestion Klin Wchnschr 6 71 23 0 1927

2965 Dohi S Heilung der Warzen durch Suggestion Jap J Dermat 30 88 1930 Zbl 36 318

2966 Memmesheimer A M and Eisenlohr E Suggestivbehandlung der Warzen Dermat Ztschr 62 63-68 1931

2967 Bonjour J La guérison des condylomes par la suggestion Presse méd 36 61 6 10 9

Chapter XLI

DISORDERS OF THE GASTROINTESTINAL TRACT

The various sections of the gastrointestinal tract are highly interdependent Gastric hyperacidity for example may lead to increased motility of the small intestine causing the chyme to be rushed to the colon before the digestion in the bowel is completed Thus toxic intermediate products may be reabsorbed and transported through the portal system to the liver where detoxification may take place provided the liver functions are unimpaired A fraction however may enter the circulation directly through the vena cava Deficiency of the antiseptic hydrochloric acid results in incomplete digestion and partial retention of the food Another important consequence is the change of the intestinal bacterial flora with ensuing putrefaction of large amounts of mucus Local inflammatory lesions may change the permeability of the mucous membranes, thus permitting the passage of toxic and allergenic substances [968 970] through the intestinal barrier though much work remains to be done to *prove* the pathogenesis of skin changes by pathological absorption

Dermadromes —Yet cutaneous symptoms arise only in a small fraction of gastrointestinal disorders No obligatory dermadrome is known in connection with gastrointestinal diseases but several dermatoses occur occasionally The percentage of skin diseases in large series of gastrointestinal cases is small Even the conditions commonly ascribed to gastrointestinal causes such as pruritus urticaria and eczema were recorded in less than one per cent of 5000 different gastrointestinal cases [971] Among 595 gastrointestinal cases [97] rosacea was observed in 3 5 per cent [2973] In some groups e g peptic ulcer or colitis the incidence of dermatoses is higher The percentages of varied gastrointestinal disorders in patients suffering from chronic eczema neurodermatitis urticaria pruritus acne rosacea and acne urticata are significant The possibility of a gastrointestinal cause should be kept in mind in persistent and unexplained cases of these dermatoses

Mouth —While the oral cavity is very often concomitantly affected by dermatoses or takes part in manifestations of internal disorders a primary mouth disease only rarely causes dermadromes In this connection one should remember the role the teeth and tonsils play in focal infections Perléche may be caused by malocclusion and ill fitting or old dentures and salivation [2193 29 4]

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[968] Urbach F Magen Darmtrakt und Haut Wien med Wchnschr 1937 I 2) 94 3 -3 6

[969] Singer G Die e dog ne Natur man her Hautkrankh iten V rh d Ges f Verd u Stoffwech elkr Vi ona pp 95-101 105-1-3 1926 Zbl 20 55

[970] Porges O Verdauu gsstörungen u d Dermatos n Wien klin Wchns hr 39 568-569 1926

[971] Bassler A The E tero-De mal Syndrome Urol & Cutan Rev 35 504 509 1931

[972] R yn A Rosacea Zbl 52 482 1936

[2973] Epstein N N Gastric Analy is in Acn Rosacea California & West Med 35 119 1 0 1931

[297] Freund H I ch bei Frwachsenen Int rlabialmykose un l ihre symptomatisch Bed utu g Arch. f Dermat u Syph 164 614-6?? 193

The shape of the lips and the tendency to form persistent wrinkles or folds at the angles of the mouth may favor localized mycotic or bacterial infection particularly in diabetics The author saw a mother of 75 years and her son of 52 years who both had a peculiarly hanging upper lip as a familial trait suffering from almost incurable perlèche Persisting eczema of the face and cheilitis even severe papillomatous forms may occasionally be caused by pyorrhea and oral ulcerations[2975] Salivation especially during the night may well cause dermatitis which according to the sleeping habits of the patient may be unilateral[115] or bilateral

Diseases of the Stomach

A great number of investigators have tried to correlate the status of *gastric acidity* with skin disease (Spiethoff[2976] and later also investigations of his pupils Ehrmann[977 298] Lejhanec after Ottenstein[9]) The results have shown that a general tendency to lowered gastric acidity exists in pruritus[976] eczema neurodermatitis[2978] chronic urticaria rosacea[297 973 2980 983] seborrheic



Fig 372 —Chronic perlèche caused by ill fitting dentures

[975]Dongen K van Zusammenhang von Krankheiten im Munde und im übrigen Körper Ztsch f Stomatol 32 1109 11 0 1934 Ztl 50 162

[23] Spiethoff B Magenstörungen bei Hautkrankheiten München med Wchnschr 59 991 191

[977]Ehrmann S Über den Zusammenhang zwischen Verdauungsstörungen und Dermatosen Wien klin Wchnschr 39 756 757 19 6

[978]Ehrmann S Über den Zusammenhang der Neurodermitis mit Erkrankungen des Verdauungstraktes und Störungen der inneren Sekretion Arch f Dermat u Syph 138 346 360 1 2

[979]Urbach E Röntgenologisch und klinische Befunde am Magen Darmtrakt bei Ekzemen und ihre Bedeutung für ein kausal Therapie Arch f Dermat u Syph 142 9 41 1923

[298] Eastwood S R Gastric Secretion and Other Digestive Factors in Rosacea Brit J Dermat 40 91 104 148 167 19 8

[2981]Stokes J H and Pillsbury D M Dermatoses and Gastric Dl a s Arch Dermat & Syph 22 962 993 1930

[2982]Piper H G Magensekretionstörung und Haut Dermat Wchnschr 110 317 323 1940

[2983]Brown W H Smith M S and McLachlan A D Fractional Gastric Analysis in Diseases of the Skin 316 Cases Special Reference to Rosacea Brit J Dermat 47 181 190 193

dermatitis moniliasis in diabetes kraurosis vulvae [984] and some other dermatoses [985] Urbach[29 9] and also Ehrmann [978] emphasized the frequent (22 per cent) finding of hyperperistalsis along with anacidity in cases of neurodermitis

Great and almost unexplainable discrepancies exist among the many reports [986 988] (also Johansen after Ottenstein[9])

Newer investigations partly allowing for the physiological subacidity of the higher age clas es [2989–990] have confirmed though not unanimously [988] that the gastric acidity tends to be subnormal in chronic inflammatory dermatoses[2983] Lejhanec after Ottenstein[9]) even if the involved skin area is relatively small [98]

The observations differ in the acute dermatoses and in the acute exacerbations of chronic skin diseases Such states seem more likely to coincide with a tendency to hyperacidity This would be in line with observations of hyperacidity after mechanical irritation radiation with ultra violet light [990 991] X ray [990] skin irritations with mustard plaster [99] and extensive burns (Diehl Jr after Urbach [968]) Very severe burns however may cause anacidity (Geber after Urbach [965]) The serum of blisters from burns or freezing with CO snow contains a histamine like substance [990] It is therefore suggestive to explain the hyperacidity as the result of release of histamine from the inflamed skin [2989 993] More difficult to explain is the subacidity in a relatively small lesion In this case skin and stomach disorders are likely to be caused by a common factor The individual constitution also has a great influence on the acidity [295] The favorable effect of HCl therapy on some skin diseases would seem to prove that the subacidity is the cause of the skin disease Unfortunately the value of this often recommended treatment is not generally confirmed [965]

Elimination of toxic substances from the skin into the stomach may be the cause for gastric ulcers in extensive burns (Kiehl Jr after Urbach [968]) though thirty autopsy reports [994] do not mention such lesions Little can be said as to whether ulcers associated with dermatitis [938–99] are due to eczema or

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[984] Gross P Non Pellagrous Erupti ns Du to D fi iency of Vitamin B Compl A ch D rmat & Syph 43 04-53 1941

[985] Ayre S J Ga t i Secretion in I o ia is E m an I D matitis H rpetiformis Arch Dermat & Syph 20 851 8,9 1929

[986] Wall S B itrag ur Aetiologi d Ek me Orvo l h tii 65 111 113 19 1 Zbl 2 289

[2987] Stokes J H a d Bee man H Eff t on th Skin of Emotional and N rvous States IV The Rosacea Compl x Arch D mat & Syph 26 478-494 193

[2988] Bergman O Koinzid nz v n Ulcus pepti um un I Hautkrankh iten Wi n klin Wchn chr 47 945-948 1934

[2989] Vos H and Vos F Verlin I u g n I r Mag nsekretion ni ht al Ursache sondern als Folge von Hautkrankheit Mü h n med W hnschr 1937 II 1456 1458

[illegible] Voss F Relation B twee Diso d rs of Secretion an I Skin D rmat Wchn chr 111 080 088 1940

[illegible] Di hl F Di Wirku g d r Ultra i I ttbestrahlung d r H ut auf di Mag nsaft kr ti n Naunyn-Schmied berg s Arch 159 367-371 1931

[illegible] A tonio M Sulla modificazi d lla secrezio gastrica per ff tto di timolazi n illa d lla region epiga tri a Arch Ital d mal d app lig r 1 184 197 193 Zbl 42 184

[993] Desaux A a d Antol E R lations ntre la peau t l tube digestif Verh 9 I t r at I ... D rmat 1 105-126 193 also 2 3 6 1936 Zbl 53 4 and 54 98

[illegible] Col brook L and oth rs St dies of Burn a I Scal I Medical Research (... Report S ries No 49 Lond 1944 His Majesty Station ry Offi e

[illegible] Lortat-Jacob L kin Diseases an I Functio al Dist ba es of Various Org ... 23 1699-170 1925

vice versa, or whether ulcers and dermatosis have a common cause The impression prevails that there exists a more than coincidental relationship

The advent of *gastroscopy* has recently revealed some relations which were not known before The gastric mucosa takes part in cutaneous lichen planus in about 20 per cent of the cases Urticaria may show in the stomach and skin simultaneously[2996 2997] Vesicular gastritis has been seen to accompany some cases of acute vesicular dermatitis In stationary eczema the gastric mucosa has usually been found in normal condition Gastritis of varying degrees of severity was present in 18 out of 19 patients with rosacea, whereas among the 15 control cases of other dermatoses only 4 patients showed evidence of gastritis[2998] In 2 patients coincidental improvement of both gastritis and rosacea could be visualized by the gastroscope

Urbach[2963] suggests that the dysfunction of the gastric mucosa may lead to increased permeability for substances from incompletely digested food which normally cannot be absorbed This may cause allergisation with cutaneous symptoms like urticaria eczema pruritus urticaria papulosa etc Abnormal absorption of allergens may also occur from gastric or duodenal ulcers

The validity of the old observations regarding the *tongue in gastric conditions* has recently been checked by Oatway and Middleton[999]

The surface of the tongue reflects the acidity of the stomach quite reliably In *hyperchlorhydria* and also in peptic ulcer the tongue is rarely smooth but often scrotal or coated Superficial defects may appear in the fur of the posterior tongue a lesion which has been related to gastric ulcer[3000] In *achlorhydria* or subacidity smoothness of the tongue is common and still more so when achlorhydria is combined with anemia The patients often complain of soreness of the tongue and a dry throat though objective changes are frequently absent

The Small Intestine

Pain distention audible peristaltic noises nausea vomiting diarrhea and constipation are the primary symptoms which characterize disorders of the small bowel (Ingelfinger in Portis[3001])

Besides the inspection of the stools chemical microscopic bacteriological and helminthological examinations should be carried out Enteritis without any involvement of other parts of the tract is relatively rare

Dermadromes —*Pruritus*[1116] urticaria and eczema have been frequently found to accompany enteritis The connection was usually demonstrated by

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[2996]Chevallier P and Moutier F L estomac des eczémateux Verh 9 internat Kongr Dermat 2 107 112 1936 Zbl 54 99

[2997]Chevallier P and Moutier F L estomac dans l eczéma vulgaire à début et à prédilection antib achieux Nutrition 6 19 54 1936 Zbl 54 598

[2998] Usher B Gastroscopic Observations in Rosacea Arch Dermat & Syph 44 251 255 1941

[2999]Oatway W S Jr and Middleton W S Correlation of Lingual Changes With Other Clinical Data Arch Int M 49 860 876 1932

[3000]Glaessner K Ueber Ulcus u go A ch Verdauung kr 51 68 73 1932

[3001]Portis S A Diseases of the Digestive System Philadelphia 1944 Lea & Febiger

the effect of dietary measures [968, 970, 300] or intestinal treatment with activated charcoal[3003] after protracted topical therapy alone had failed Protein putre faction and carbohydrate fermentation could frequently be demonstrated in the feces in eczema especially perianal eczema acne, urticaria pruritus[3004] and in fantile eczema [300] The bacterial flora produces porphyrins the light sensitizing property of which is well known

Urinary indoxyl a ign of intestinal putrefaction was not found increased in 42 cases of eczema [3006] Vaccines derived from fecal bacteria have been found useful in the treatment of some dermatoses but this method has not found much acclaim from dermatologists Achylia gastrica and enteritis may be followed by the accumulation of feces and mucus in the cecum with subsequent inflammation This typical syndrome of *typhlitis* (cecitis) [970, 3007] with dull pain in the ileocecal region is often mistaken for appendicitis Neurodermatitis lichen urticatus urticaria and eczema have quite frequently been found associated with typhlitis These dermatoses disappeared after treatment of the typhlitis with HCl and a diet free of irritating cellulose fibers [2968, 2970, 97] Creosote has been advocated as an intestinal disinfectant

Sprue — Sprue is a disease of the small intestine characterized by func tional motor disorders and impaired absorption of foods particularly fats' (Ingelfinger in Portis[3001]) The cause is not known but a nutritional deficiency probably resulting from a protracted diet deficient in vitamin B complex and in proteins and too rich in carbohydrates is suspected Manson Bahr[3008] empha sizes the importance of preceding intestinal infection Progressive weakness, mental depression severe macrocytic anemia muscular wasting and emaciation are typical of fully developed cases [3009] In contrast to pernicious anemia the stomach usually contains free hydrochloric acid The most important features are diarrhea with pale greasy foul smelling unformed watery stools, cramps and distention Secondary deficiencies develop particularly of the fat oluble vita mins The characteristic pathologic changes are atrophy of the intestinal mucosa and extreme depletion of the fat reserves of the body Not too far advanced cases respond to liver therapy in a way similar to pernicious anemia

The disease is common in some tropical countries particularly India and China but as is now known a probably identical disease is not rare in the tem perate zones of Europe and America The infantile form is known as celiac disease

[3002] Aitken R The R action of the Stools and It Relation to Diseases of the Skin Brit J Dermat 51 13 17 1939

[3003] Csillag J De matitis Follicularis Hype keratotica Prurigino a Circumscripta—Successful Treatment With Charcoal Zbl 35 453 1931

[3004] Schwartz H J Associ tion of Intestinal Indigestion With Various Dermatoses Arch. D rmat & Syph 13 6 -674 19 6

[3005] Montlaur H and Coutl're S Les modificati s chimiques des selles au cours de l évolution de l eczéma chez le nourrisson Bull Acad Med Paris III 104 91 93 19 0

[3006] H rman E H a d B H fante J G Elweissfäulnis und Hautkrankheiten Nederl tijdsch v geneesk 1930 I 1316-1331 Zbl 35 40

[3007] Porges O Ueber d n Zusamm nha g von Dünndarmkatarrh und Dermatosen Wi n. klin Wchnschr 1932 I 251 25

[3008] Manson Bahr P and Will ughby H Sprue 200 Cases Quart J Med 23 11-442 1930

[3009] Hanes F M Spru in H A Ch i ti n s O ford Medicine vol. 5 New Yo k 1939 O fo d University Press p 631

Dermadromes —The long known[3010] importance of the mucocutaneous manifestations of the sprue syndrome has recently been re emphasized by Kauf man and Smith[3011] Glossitis probably reflecting similar changes in the intestinal tract is very common and if combined with characteristic diarrhea is suggestive of the disease

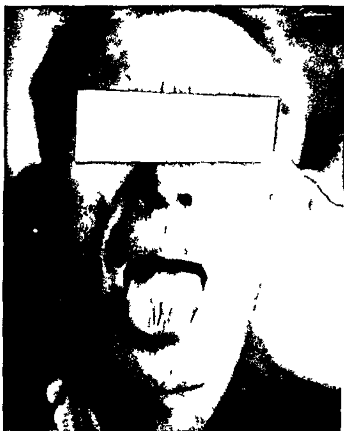


Fig 373 —Sprue Atrophic glo itis and fa ial pigmentation (From Manson Bahr Sir Philip Quart J Med)

Stomatitis and glossitis occur in more than 75 per cent of the cases[3012 3013] often preceding anemias [464] The tongue changes involve at first the edges and the tip later the entire surface starting with aphthae or minute shallow ulcers along the edges[3013] and inflammation of the fungiform papillae The sense of taste is often lost in acute sprue and salivation is increased The glossitis may precede the diarrhea The tongue is extremely tender especially in the presence

[3010] Bahr P H A Report on Researches on Sprue in Ceylon 1912 1914 London 1915 Cam b idge *University Press*

[3011] Kaufman W H and Smith D C Cutaneous Changes in Sprue Syndrome J A M A **121** 168 173 1943

[3012] Thaysen T E H Ten Cas s of Idiopathic Steato hea Qua t J Med **4** 359 395 1935

[3013] Low G C Sprue 150 Cases Quart J Med **21** 5 3 534 1928



Fig 374 —Spru Chloasma perioral (From Kaufman W H and Smith D G J A M A 1913)

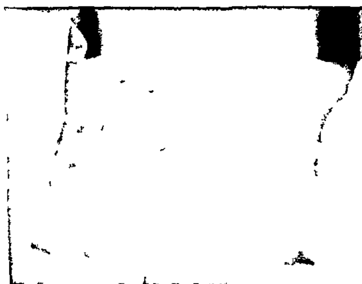


Fig 3 5 —Sprue Pigmentation of abdomen (From Manson Bah Sir Philip Quart J Med)

of aphthous ulcers There often are indentations of the edges of the tongue caused by the teeth Atrophy of the tongue with complete disappearance of the fungiform papillae occurs later [3008 3010] In such cases the tongue is narrow and pointed

The fully developed picture shows absence of the filiform papillae with the fungiform papillae remaining as prominent shiny sometimes hemorrhagic points [464 3011]

Painful rhagades may cut the tongue in both directions Fissuring of the angles of the mouth is also common Buccal and infralingual aphthae have been found varying from 22 5 to 67 per cent in large series [3005 3013]

The skin is pale dry flabby grayish yellow but not icteric Large freckles and symmetric chloasma like patchy or diffuse pigmentations have been recorded Even Addison s disease is sometimes suggested Some degree of pathologic pigmentation was seen in the majority of the well-observed cases [3008 3011 3012] Pellagroid pigmented patches on the dorsa of the hands have also been seen [3011 3012] The pigment was found iron free thus probably being melanin The pigmentations in sprue seem to improve with treatmen [3008] of the disease

Intestinal polyposis may be associated with jet black melanin pigmentation in dots and spots about the mouth the lips and over the hands [668] Similar pigmentations have been seen in *gastrojejunocolic fistula tuberculosis of the ileum celiac disease* Jeghers[668] believes that pigmentation without pellagra is more pronounced in diseases of the small intestine than in disorders of the colon Urbach[16] suggests that the oxidation of phenol substances possibly also of skatol may lead to excessive melanin formation though no proof for this probability has been offered as yet

Ulcerative Colitis —Nonspecific ulcerative colitis is in about 2 to 3 per cent complicated by skin lesions [3014 3015] Most troublesome and conspicuous are ulcerations which may occur[3016] on the lower legs They increase rapidly in size after taking on a kidney shape They are painful and quite deep but the healing tendency is marked The appearance and disappearance of the skin lesions may reflect the course but not the extent of the colitis [59 3014 3017]

The author observed a case of ulcerative colitis in a woman who after an unhappy married life went through the excitement of a divorce The periods of worry and excitement not only produced acute attacks of colitis but also new and severe ulcerations of the legs

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[3014] Bargen J A Complications and Sequelae of Chronic Ulcerative Colitis Ann Int Med 3 335 352 1929

[3015] Bargen J A Present Status of Colitis and Regional Enteritis Bull New York Acad Med 20 34 35 1944

[3016] Brunsting L A Goeckerman W H and O Leary P A Pyoderma Gangrenosum Arch Dermat & Syph 22 655 680 1930

[3017] Jones C M Peripheral Complications of Ulcerative Colitis Med Clin North America 16 919 928 1933

Pigmentations of the face and body also of the dorsa of the hands may occasionally take on the characteristics of sprue or pellagra Thickening and distal loosening of the nails may occur[3018]



Fig 376 —L g ul in ulc rative colitl (Courtesy D J I Jat k lso)

Dryness and scaliness follicular keratosis symmetrical atrophy pigmentations various erythemas and cheilitis have been observed and at least in part have been interpreted as avitaminoses[3001 3014 3017 3019]

Tongue and buccal changes occurred in 60 per cent of Mackie s[3019] 75 cases They may correspond to those in sprue There was accentuation of the papillae fungiformes strawberry tongue in the earlier stages and smooth atrophy later In severe cases a stomatitis indistinguishable from that in pellagra may develop

[3018] Mi t J J l yod rn a C gee osum Ony h gryphos and O ych ly i With Colitis Arch D rmat & Syph 40 541-543 1939

[3019] Macki T T U l ratiy Colitis II Th Factor of D fici cy States J A M A 104 1 ,-1 8 1935

Whitfield[3070] called "dermatitis colonica a parapsoriasis like eruption of discrete flat red macules with telangiectases and pigmentation He connected the dermatosis with colitis and an abundance of streptococci in the stools

Urticaria seems to be relatively common in colonic disease[3071] The author observed the first outbreak of psoriasis in a man of fifty in typical localization immediately after a *colostomy* had been performed because of rectal cancer The patient remained well for two years but never recovered from his psoriasis Pruritus without visible skin lesions has been seen in patients with colostomy stomata



Fig 377 —Coliti ulcerosa Female aged 32 years Multiple kidney shap d rapidly progre sing and healing ulcers of the legs Rema kat le parallelism of course of th severe colitis and the ulcerations Both subject to psychog ni influence as demonstrated during the exc tements of divorce proceedings Discoloration of th skin i partly due to gentian violet (Patient of Dr Greenberg)

Treatment —If certain dermatoses are caused by pathological contents of the bowel it seems logical to try to treat such skin lesions by the cleansing of the intestinal canal with laxatives increased intake of water and enemas These methods are not much used today However in urticaria and pruritus catharsis is worth while trying The use of saline cathartics seems satisfactory In spite of the good experiences of some authors[3072] colonic irrigation has not become a generally accepted method of treatment Urticaria lichen urticatus pruritus

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[3070] Whitfield A On a Hitherto Undescrib d Disease of the Skin Brit J Dermat 44 24 9 1932

[3071] Bockus H L Bank J and Wilkinson S A Neurogenic Mucous Colitis Am J M Sc 176 813 829 1928

[3072] Urbach E Das subaqual Darmbad in de D rmatologie Arch f Dermat u Syph 159 523 540 1930

and toxicodermas seem to be the dermatological indications for the use of this method The technique is well described by Urbach[30m] and by Read[30 3] Large doses of activated charcoal to absorb toxic products in the bowel may be used for the same conditions[30 4]

The most important method of treatment consists in the proper diet for which the textbooks of gastroenterology and nutrition may be consulted Very recently Urbach[16] has presented an excellent modern treatise on the dietary treatment of dermatoses including those of gastrointestinal origin

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[30 3] Read H S Colonic Irrigation Med Physics p 264 1944 The Year Book Publishers Inc Chicago

[30 4] Czillag J Dyspeptische Hautkrankheiten Zbl 35 337

Chapter XLII

DISEASES OF THE LIVER AND PANCREAS

The Liver

The bile the secretion of the liver contains bile pigments bile salts cholesterol lecithin and mucin [1339] The pigment bilirubin is a waste product from destroyed erythrocytes which have been collected by the reticulo-endothelial system The liver takes bilirubin from the blood and secretes it into the bile Bilirubin which has passed the liver is slightly different from blood bilirubin This is demonstrable by the two van den Bergh reactions Biliverdin is an oxidation product of bilirubin The bile salts facilitate the action of the pancreas and the absorption of fatty acids Cholesterol is a lipid of the sterol group mainly derived from animal fats The liver supplies most of the blood sugar and forms all the urea It synthesizes most of the fibrinogen thus playing an important role in blood coagulation

Liver damage may result in hemorrhagic disease with prolonged clotting time and prothrombinopenia [1890] The liver has a significant detoxifying function Many metabolic and external poisons are either destroyed in the liver or excreted into the bile Disturbance of the detoxifying function of the liver plays an important role in the pathogenesis of allergy The liver is often called the second barrier against poison the first being the intestinal wall [159 30]

Dermadromes —*Jaundice* may be caused by *obstruction* in the common duct or in higher parts of the bile duct system provided the dammed up area is large enough The bilirubin is then reabsorbed into the blood There are many causes for such an obstruction the most important being gallstones neoplasms scarring or inflammatory swelling

In *toxic or infective jaundice* the bilirubin secretion of the liver cells is disturbed Therefore the blood cannot be sufficiently freed of its bilirubin which soon reaches an icteric level Toxic or infective jaundice is the most common form of jaundice [85] It is encountered in yellow fever Weil s disease typhoid fever pneumonia and other infections in poisonings from chloroform gold arsenobenzol phosphorus carbon tetrachloride some mushrooms e g helvella and a great variety of other toxic agents

In *hemolytic jaundice* the rate of bilirubin production from destroyed red cells exceeds the capacity of the liver to excrete it The urine as well as the feces retain normal color Some forms of hemolytic icterus are hereditary

These causes of icterus are not always sharply divided Thus e g obstruction may lead to absorption of bile but also to infection and damage to the liver

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[85] Urbach F Über die wechselseitigen Beziehungen zwischen Leber und Haut Arch f Dermat u Syph **175** 767 787 1937

cells with subsequent failure to drain bilirubin from the blood Jaundice is probably the most regularly encountered skin manifestation of any internal disorder

The color of jaundiced skin varies widely from a slightly yellow tinge to lemon greenish brown or even purplish shades Greenish jaundice is explained by cyanosis brown or black hues come about by combination with various pigmentations Orange or saffron color of the skin suggests intrahepatic jaundice greenish to bronze obstructive jaundice A greenish tint may develop in intrahepatic jaundice in the presence of liver necrosis and also in the receding stage of jaundice [306] Yellowish blue or green is considered almost diagnostic of a tricuspid lesion or a relative insufficiency of the valve (Wearn after Jeghers[668])

The distribution of jaundice is not always even In slight and early cases only the sclerotics or the hard palate may appear yellow In catarrhal icterus the discoloration usually appears on the head neck the upper trunk the abdomen the legs and finally on the forearms and hands [2097] The jaundice may come on in repeated attacks each increasing the color of already yellow areas At the height of the icterus the areas which appeared first are then the darkest Thus the upper part of the body is generally darker than the lower part [306 8 3030] The regression of icterus follows the reverse order of its appearance so that sclerotics and face may still be yellow when all other parts have reached a normal color The differences in intensity are not yet sufficiently explained Differences in concentration and in the amount of blood which during a given time flows through and stains the areas are likely to cause difference of intensity of color

Hyperemia or urticaria causes local increase of the icterus probably because of greater capillary permeability this is easy to demonstrate under glass pressure In subclinical icterus the hyperemic halo of a histamin reaction leaves a yellow ring after the hyperemia has disappeared With this skin test a bilirubin level of as low as 1 mg per cent can be shown [303] The remaining local icterus after disappearance of urticaria factitia is called yellow dermographia [303] It may be present prior to clinical icterus Two cases of contralateral jaundice and ipsolateral edema in apoplexy and cardiac decompensation have been described by Page [641] It has been suggested that in these instances the edema prevented the entrance of the pigment but this is unlikely since a local edema like a wheal increases icterus

Localized jaundice about the umbilicus due to rupture of the common bile duct was described by Rausehoff (see Teghers) [669]

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[306]Lichtman S S Di eases of the Li r Philadelphia 194 Lea & Febig r

[2097]Ko acs F L be die V rt ilu g des II tikt ru Wi n klin Wel nschr 19 8 II 14 6-14

[8]t rol F a 1 Po enberg M R gionäre Ikt rus D ut h med Wchnschr 54 90-91 19 8

[3030] hl k B Di V teilung i (ell fä l ung in d r Haut beim Icterus neoatorum Zt hr f Ki le h 38 513 5 0 1924

[3030]M yirl f r E M i1 Reg l 1 r fraktio l rte Absätti ung im V rhältn l zum Hautikt rus Wi n klin W l sch 19 31 73

kl in O \ chwei o l t t m I t rus durch intra1 rmal Hi taminin jection Klin Wch ct 1931 11 203 03

[303]D bes V J a 1 Eng lhar lt H F Y llow D m graphia Arch D mat & Syph 48 310-311 1943

Several tests using injection of dyes into the skin have been devised to demonstrate subclinical icterus[3033] but none has become important since accurate quantitative determinations of bilirubin in the serum are now generally made with the van den Bergh method Intracutaneous injection of 1 per cent potassium ferricyanide produces a blue spot if the icterus is caused by an iron containing blood derivative This is known as the positive Brugsch test[3034] Bilirubin is iron free The value of the Brugsch test for iron has recently been doubted[3076] The extrahepatic type of icterus is seen in the presence of very numerous skin hemorrhages which may cause generalized yellow discoloration The Brugsch test is also positive in icterus neonatorum

Itching sometimes restricted to some areas is a common and troublesome though not invariable symptom of icterus It is absent in hemolytic icterus[303] It is controversial whether the presence of bile salts and bilirubin is responsible for the pruritus Insulin in doses of 20 50 units daily seems to relieve the itching[3036] In senile and other types of pruritus sine materia tests sometimes indicate an impaired liver function[3037]

The capillaries of icteric skin are more permeable than those in the normal skin

Urticaria is frequently seen The icteric skin develops a wheal after injection or iontophoresis of a one hundred times weaker histamin solution than is necessary to create the same effect in the normal skin[1006] Cantharides draw blisters in a shorter time in icteric than in normal skin[3038]

The disappearing time of an intracutaneous wheal of isotonic salt solution (McClure and Aldrich Test[169]) is shortened in icterus[3039]

Long lasting jaundice with hypercholesterolemia as in biliary cirrhosis may produce *xanthomas* in the skin One has to look for these lesions in the creases of the finger joints and about the elbows These xanthomas are reversible with changes in the blood cholesterin[3040]

Liver spots are chloasma like hyperpigmentations in the face caused by melanin deposits They are suggestive of liver disease but are neither frequent nor specific The French term masque biliaire is applied to a periocular chloasma hepaticum

The *hemorrhagic tendency*[504] may be severe however it is not parallel to the icteric indexes[890] It constitutes an added risk in any surgery on a jaundiced patient Gastrointestinal bleeding is usually the first hemorrhagic symptom in obstructive jaundice An alarming picture of hemorrhagic disease

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[3033] Dad l C Sulla l r a della bili ubina nella p lle d gli itteri l Riv di clin med 32 501 506 1931

B ug h T Zu Analy d s Ikteru Deutsch med Wch schr 19 9 I 687-688

[3035] Ro enthal F Hautju ke b i Ikt us Th rap d G genw 70 297 301 19 9

[3036] Malamu l T In ulin beim P u itus I Ikteru kra ken P ensa méd a gent 17 1 34 1936 1931 Zbl 38 484

[3037] Hüt ner K Hyperbili ubi m e u I ru itus A ch f D mat u Syph 275 508 514 1937

[3038] D Tullio R La pe m al ilità d cap lla i l indl inflammatario d lla cute negli epato p i nti Rifo ma med 44 341-344 19 8

[169] Mo a J M and Al ka F J Th Effe t of Jaun li on Intrad mally Inject l Salt Soluti J Lab & Clin Med 20 719 7 ? 193

[304] Comf t M W Shepa d V O and S ll A M Xanthomatous Biliary Ci rhosis Proc Staff Met Mayo Clin 16 3 4 377 1941

may follow[890] Quick emphasizes the absence of petechiae and the presence of large ecchymotic areas

The lack of vitamin K which maintains the normal level of serum prothrombin is now recognized as the cause of the hemorrhagic disease in obstructive jaundice with not too much damage to the liver[890 3041]

Extensive liver damage whether primary or secondary may account for the inability of the liver to produce prothrombin The resulting hemorrhagic tendency is due to hypoprothrombinemia and is not relieved by vitamin K[890 1776]

Cirrhosis of the Liver —In portal cirrhosis the skin is usually grayish or sallow Icterus often little pronounced is seen in 30 to 65 per cent of the cases[404 3043] Pruritus is common Urbach[307] has produced considerable evidence



Fig 3 x —Cirrhosi f th liv r Larg ascul r spi[ ] r a[ ] o e th la[ ]iel surrou [ ] [ ] y s [ ] al small pil rs (F o n B an W B Medicin)

tracing the pruritus in hepatic cirrhosis to the disturbed protein metabolism of the liver While there are no conspicuous dermadromes the frequent appearance of spider like telangiectases is of theoretical and to some extent prognostic interest

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h a k R R Th Di gnosi an l Treatm nt of tl Purp ric Diseases South M J 34 56-61 1341

[ ]Fagi J D a l Th mpso F M l Cases f C l hosi of th Li e An I t M l 21 [ ] 1344

[ ]atn R O D a I l at k A J J Th Natural Hi tory f La [ ] ec s Cirrhosis of th Li r Analy i of 3 6 Cases M [ ] li in 21 [ ] 2[ ] 1942

PLATE VI

1 Herpes simplex as seen in many fevers

2 Hepatic cirrhosis Ascites congested veins axillary alopecia pigmented male nipple Note absence of striae

3 Hepatic cirrhosis Erythema of the palmar eminences so called liver palm and vascular spider in unusual location

4 Hepatic cirrhosis Vascular spider

5 Biliary cirrhosis Four years after ligation of common duct jaundice

6 Biliary cirrhosis Bleeding gums decayed teeth



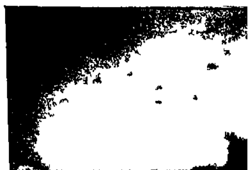





PLATE VI

Vascular spiders (cutaneous arterial spiders[3044] nevus araneus like or stellate lesions tache stellaire etoile vasculaire) were first described in an alcoholic (hepatic cirrhosis) by Erasmus Wilson[3045] Their physiology histology and clinical significance has recently been studied by Patek Jr Post and Victor[3046] Bean[3044] and many other authors particularly French

The vascular spider consists of a body which is a central raised pin head to lentil sized papule from which the legs spokes or radicles radiate The latter are telangiectases which branch out and anastomose in many ways An area of erythema often surrounds the central punctum and an anemic halo around the red area is occasionally visible The color of the central eminence is bright red but does not show well in infra red photography[3044] which is one of the proofs of its arterial nature Veins appear darker in infra red The temperature of the vascular spider is 2 3° C (3 5 F) higher than the normal skin surface The blood flows from the center to the periphery and pulsation can usually be demonstrated if controlled glass pressure is applied The intravascular pressure as measured by the force necessary to stop the pulsation and blanch the lesion is between 70 and 90 mm of Hg Adrenalin blanches the finer ramifications and histamine deepens the red area more than the adjacent skin The number of spiders varies from a single one to an occasional exanthem of the density of mild chicken pox This however is rare The spiders are with few exceptions restricted to the upper half of the body with a predilection for the neck clavicular areas and face The pattern of distribution reminds of sites of benign new growths under estrogenic influence (see pregnancy and menopause) The palms are more often affected than the arms Scattered or reticular fine telangiectases may be seen together with the spiders indicating the widespread alteration of the capillaries Bean[3044] aptly compares this type of telangiectasis with paper money flecked with silk threads

Besides the nevus araneus like lesions simple telangiectases in small plaques at the costal arch were described by Galloway[3047] in various visceral conditions with stasis including cirrhosis

Stellate telangiectases in cases of Laennec s cirrhosis have been found in 15 per cent by Ratnoff and Patek[3043] 56 per cent by Cirovacki (after Bean) and 75 per cent by Bean[3044] but they are also encountered in other liver diseases e g in catarrhal jaundice in Weil s disease and in common duct stone with jaundice though decidedly less often[3044] The chronicity of the disease does not seem to have much bearing on their development since they have rarely been found in hepatic carcinomatosis It can generally be said that the presence of spiders indicates a more severe cirrhosis[3044] Improvement of the hepatic condition may be followed by disappearance of the spiders

The histological[3044 30 6 3048] character of the spider is that of a coiled artery larger than that ordinarily found in the surface of the skin The arterial wall has

[3044] Bean W B The Cutaneous Arterial Spider A Survey M ... 243-331 194
[3045] Wilson E ... Eruptio Angiomata J Cut Med & Dis Skin 2 ...
[3046] Patek A J Jr Post J and Victor J C The Vascular Spider Associated With Cirrhosis of the Liver Am J M Sc 200 341-34 1940
[3047] Galloway J ... Visceral Diseases Brit M J 1908 I 60-66
[3048] Wegelin C Cirrhosis of the Liver With ... Teleangiectases of the Skin Schweiz Ztschr f Path u Bakt 8 374-3 194

some characteristics of the arterial segment of an arteriovenous anastomosis (glomus) The spider is decidedly different from a hemangioma

The free urinary *estrogen* values in advanced cirrhosis are high and the androgen values are low [1410] The diseased liver seems unable to inactivate



Fig 379 —Hepatic cirrho is gynecomastia



Fig 380 —Hepatic irrh i pigm nt d a l e la ge l male nipi l

estrogens[3049] and the testicular atrophy which is common in fully developed cases probably accounts in part for the lack of androgens Androgens continue to be inactivated by a liver which has been damaged enough to be unable to inactivate estrogens Thus the balance between estrogens and androgens is upset[3049] These endocrine disturbances help to explain the production of spiders palmar erythema and chloasma which also occur in pregnancy and which can be provoked by administration of estrogens to cirrhotic patients[3050, 3051] The low level of androgens may increase the effect of the high estrogens This may also account for the gyne



Fig 351 —H p ti irrho i Axillary al p cia nla ged m ale nipple

comastia which is frequently present in advanced ca es Paula[3052] found gynecomastia with increase of milk ducts cyst formation and milk secretion in 5 out of 7 autopsies[1410, 3052] The *nipples* are often enlarged cylindric and erect the areola deeply pigmented The *loss of axillary* and to a les er extent pubic hair[3053] is common in cirrhosis This symptom may also be related to endocrine disturbances especially testicular

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[3049] Biskind M S Biskind G R and Biskind L H Nutritional Deficiency in the Etiology of Menorrhagia Metrorrhagia Cystic Mastitis and Premenstrual Tension II Treatment With Vitamin B Compl Surg Gyn ec & Obst 78 49 7 1944

[3050] Bean W B A Note on the Development of Cutaneous Arterial Spiders and Palmar Erythema in Persons With Liver Disease and Their Development Following the Administration of Estrogen Am J M S 204 1 3 194

[3051] Bean W B Acquired Palmar Erythema and Cutaneous Vascular Spiders Am Heart J 25 463-477 1943

[3052] Paula F Gynäkomastie und Lebercirrhose Deutsches Arch f klin Med 169 83 99 1930

[3053] Martí F Sy tém pil u ill re J v m l la Rom 51 6 4 1931 Zl 39 768

Erythema of the palmar eminences (liver palms) especially of the hypothenar often associated with spiders was observed in about 25 per cent of the patients with cirrhosis[30 4] but only in 4 per cent of Ratoff and Patek's[3043] 386 cases. The condition also occurs in other internal disorders e g gastrointestinal ulcer rheumatoid arthritis heart disease chronic sepsis pulmonary tuberculosis chronic deficiency states and in pregnancy. It is also occasionally seen in normal persons. Palmar erythema like its related lesion the vascular spider may wax and wane with fluctuations in the severity of the liver disease.[3051] It has been



Fig 38 —Hepatic cirrhosis axillary alopecia Male aged 50 years

shown that palmar erythema can be provoked by potent estrogens in persons having some of the mentioned diseases.[30 0] The erythema is arterial in character and warm to the touch. The capillaries are increased. The palmar erythema is sometimes combined with erythema of the fingertips clubbing of the end phalanges and Hippocratic nails.

The well known appearance of *dilated veins* around the navel (caput medusae) is relatively rare. Congested veins are of frequent occurrence in the presence

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[3054]Perera G A A Note on Palmar Erythema (So Called Liver Palms) J A M A 119 1417 1943

of ascites[3043] In more than 40 per cent of the cases[304] dilated veins in the skin of the abdominal and thoracic walls show the existence of an established collateral circulation Infra red photography may detect tortuous veins before they become visible Edema of the ankles occurs in the majority of the cases Hemorrhoids are seen more frequently in cirrhosis than in comparable groups (Chapman Snell and Rowntree after Ratnoff and Patek[3043]) *Hemorrhagic* phenomena are observed in about 25 per cent of the



Fig 383 – Biliary cirrho is Sli h to gue



Fig 3 4 Xa th m h l n a p lpst arum l pati nt with biliary cirrhosi

cases of cirrhosis One third of the hemorrhagic patients show purpura[3043] Striae are absent

In *biliary cirrhosis* the jaundice is severe Bleeding from the gums is frequently seen Xanthomas in the palmar creases the soles and elsewhere may develop in hyperlipemia[3055]

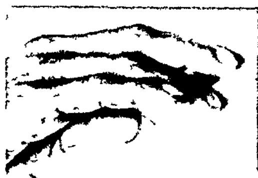


Fig 38 —Cachexia (biliary cirrhosis) Hippocratic nails

Gallstones and Cholecystitis —Little is known of skin manifestations in diseases of the gallbladder The infected gallbladder may become a focus of infection and cause cutaneous lesions[30 6] A stone in the common duct may cause icterus with its cutaneous sequelae Xanthoma especially of the lower eyelid salivation gingivitis transient yellow or persistent chloasmatic spots on forehead and cheeks urticaria[30] pruritus and telangiectases are occasional manifestations of chronic cholecystitis[30 9]

The Liver in Dermatoses —Many investigators[3059] have studied liver functions in skin diseases This has been done with most of the liver function tests (for a practical appraisal of the liver tests see Ivy and Roth[3060]) especially the two van den Bergh tests the determination of urobilin and urobilinogen in the urine blood sugar tolerance tests galactose gelatine and water[3061] phenol tetrachlorphthalein sodium[306] Widal s hemoplasia[3063] Falta s bile tolerance test

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[3] Eust rm C B a d Montgome y H Disorders of Live an l E trahepatic Biliary Ducts As ociat 1 With Cuta eous Xanthomas an l Hyp rl pemia Gastroe terology 2 27 86 1944

[3056]La C W a l St oud C M I yo l rma Gangreno um Arch Dermat & Syph 27 460 468 1933

[3]M agh I R I tiology a l Re ults of Treatment in Angio urot c Edema and Urticaria J A M A 90 668 671 19 8

[30]Dal a J D juel (u sigi s bu caux t cutanés la s le chol cystites t l s ulcère duodenaux Bull méd 1931 II 9 096 Zbl 41 78

[3] Dul owy M I or l tion z l cl n Haut und Leber D matologi a 79 370-391 1939

[3060]Ivy A C and Roth J A Why do a Liv r Function Test? Gast o nt rology 1 655-669 1943

[3]D ilk n H L f fu kti p üfu g in d r D matologi Arch f Dermat u Syph 168 49 504 1933 180 456 463 1331

[306]Matsunobu F Ekzema an l Liv Fun tio Ecz ma a l Sugar Metaboli m Jap J D rmat 30 8 838 1030 Zbl 37 35

[3063]Jjichi K Li l u tion in Skin D as s Jap J D mat 35 611 632 1934 Zbl 49 491

and the determination of urobilinogen in the stools after Schmidt [30 9] Other investigations were concerned with the reticulo-endothelial system of which the Kupffer cells in the liver represent an important part The disappearance of intravenously injected congo red from the blood (Adler and Reimann test) was used as an indication of the function of the reticulo endothelial system in the liver [3059] The reticulo endothelial system of the skin was studied in this connec tion by von Leszczynski and his collaborators[30 9] mostly with intracutaneous injections of histamin morphin caffein pilocarpin and trypan blue The results of the many investigations of liver function in dermatoses are not consistent Hepatic dysfunctions were found in eczema [306 3064 3066] acute exudative derma toses [3061] urticaria dermatitis after arsphenamines [0 5 3061 3063] and other drug eruptions [3067] In the larger series the patients with disturbances ranged from 10 to 40 per cent The high incidence of liver disorders in photodermatoses drug eruptions rosacea and other dermatoses characterized bv widespread new for mation of capillaries is emphasized by Milbradt[3068] and many others

Porphyrinuria and increased fecal porphyrin which often accompany photodermatoses e g hydroa vacciniforme is probably the expression of a dis turbed liver function [16 30f9 3072] The combination of alcoholism and syphilis is apt to create the conditions which lead to hepatic cirrhosis porphyrinuria and photodermatosis In porphyrinuria and hydroa the mechanical vulnera bility of the skin may be much increased so that slight trauma may cause blisters and oozing defects [307 3073] Thus an epidermolysis bullosa like picture may ensue [3074 3076] Photodermatoses with an hepatic background and hyperpor phyrinemia or porphyrinuria may also appear as xeroderma pigmentosum [3077] eczema urticaria erythema multiforme and prurigo

Xanthomas including the common xanthelasmas of the eyelids should always arouse the suspicion of liver disease Icterus is frequently found in xanthoma and even in its absence liver disorders may well be detected by func tion tests (Hubner after Urbach[30 8])

[3064] Fal hi G Ric chi n lla fu zio litä p tica n ll ecz ma Gi r Ital di i rmat e sif 68 704 19 7

[5] I ordowich F Bluthilirubi bestimmugen I i Hautk ankh it n Ar h f D rmat u Syph 175 117 I 1937

[3066] M quardt Porphy in im U in b i Haut krankung n Zł I 53 5 5-5 6 1936

[3068] Milbradt W H ut und Org nstöru g n L b rstoffwech I Med Welt 9 1417 14 1 1935

[306] Carri C Hydroa va iniform un I Po pl yrinuri A ch f De mat u Syph 163 5 3-543 1931

[3?7] St asser and Urbach Hydro acci ifo me mit I orphyrinu I Wi med Wchuschr 1931 II 1506 150

[3071] Brun ti g L A B ug h J T an I O Leary P A Porphyrin Metabolism in Di a of the Ski Arch Dermat & Syph 39 94-30 1939

[3072] Urba h F Hy I oa cci iform i Leb r und Milzcirrhose P phyri u i Zł I 53 140 1936

[7] Urba h F an I Bloch J Hydroa Vacci if m Po phy i p thi H patopathi Wi n klin Wchnschr 47 7 53 1934

[7] Cottro H and Elli g r F P phyri Arch f Dermat u Syph 164 11-43 1931

[3077] Gottron H Epi I moly i I B sa-artiges I rankh it i ll i bei Porphy ia D mat Wchnschr 101 1305 1935

[3076] Turner W J and Oberm yer M E P rphy ia With Epi I moly i B llo a Hypertri t sis a d M lano I Arcl Dermat & Syph 37 549-572 1938

[3077] Blum thal Xerod rma pigm tosum avec épith lioma d types divers Bull S c f an D rm t 2 74 6 1931 Zł I 39 6

[3078] Urba h F hw te Licht I matosen auf Gru dlag von isoliert r pathol gisch r I rphyri bil lung im D rm i folg Dysbakt ri und H patopathi Klin W hns hr 17 304 310 193

Clinical experience has often shown that psoriasis eczema urticaria[305, 3057, 3079] Quincke s edema rosacea and other dermatoses followed the ups and downs of liver or gallbladder disease and cleared up after their successful treatment An impressive group of such cases was presented by Smithies[3080] who used drainage of the duodenum mostly combined with a diet low in fat and protein and stimulation of the flow of bile by magnesium sulfate

The opinions about associated liver disturbances in psoriasis are diver gent[3061,3063] The possibility of *liver damage secondary to skin disease* must be recognized This is based on observations in burns and in the experimental croton oil dermatitis of rabbits[306] Dubowy[3059] found hepatic dysfunction regularly connected with a disturbed RES of the skin

Liver extract has been found a useful adjunct in the treatment of many skin diseases[3075] Exfoliative dermatitis due to arsphenamine is an example

The Pancreas

The pancreatic juice neutralizes the gastric acidity splits proteins down to amino acids (trypsin) fats into glycerine and fatty acids (lipase) and converts starches into sugar (amylase). The best known hormone of the pancreas is insulin which helps to burn sugar stimulates the formation of glycogen in the liver and muscles and probably inhibits glucose formation from amino acids in the liver[1339] In pancreatectomized dogs the liver becomes fatty This can be prevented by an alcoholic extract of pancreas Dragstedt s lipocaic[1989]

Kallikrein (padutin) is a pancreatic hormone with a vasodilating effect It can to some degree neutralize the effect of adrenalin The most important skin manifestations of pancreatic disorders are those occurring in *diabetes* (see chapter on diabetes) Our knowledge of other pancreatic dermadromes is scanty

Dermadromes of Pancreatic Diseases —Chronic pancreatitis and other benign disorders may provoke urticaria[3081] eczema pruritus ani[308] and other nonspecific dermatoses The disturbance of fat digestion has been related to some cases of eczema[3083] especially in infants[3081] The administration of pan creatic substance by mouth has been recommended

Acute necrosis of the pancreas (acute pancreatitis) is occasionally accom panied by deeply cyanotic livedo like or spotty venous patterns (Walsted after Moynihan[308]) covering the abdomen chest and thighs[3085] A palm sized dirty

[3079] S hur H Urticaria und Cholelithiasis Wien klin Wchnschr 40 81 83 19-7

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gray green slightly raised discoloration has been observed around the navel or in the lumbar area probably caused by direct leakage and autodigestion This is known as *Turner's sign*[3085 3087 3088] The abdominal cyanosis is not seen in the majority of the cases[3089] It is considered a pathognomonic sign

Cancer of the head of the pancreas causes intense obstructive sometimes blackish jaundice (ictere noir)[1878] In 56 per cent of the autopsied cases of cancer of the body or tail of the pancreas at least one thrombosis was found[3090] In about one third of the cases the venous thromboses were widely disseminated Usually there was no jaundice present Thromboses of veins in both lower legs with acute cutaneous inflammation may be the presenting symptom of carcinoma of the pancreatic body[3091] No mention of thromboses is made in a recent review of 52 cases of pancreatic carcinoma[309] The thromboses may affect any of the great veins of the body The neoplasms were all of the mucinous type

Pancreatic extracts especially lipocaic and depropanex have given encouraging though not striking results in psoriasis[3093 3094]

The insulin free pancreatic extract padutin or kallikrein[3095] and similar preparations[1988] has been used in Raynaud's disease acrocyanosis and related peripheral vascular disorders It has also given some results in scleroderma[3096] of the morphea type

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CHAPTER XLIII

DISORDERS OF THE RESPIRATORY TRACT*

Generally the *incidence* of dermatoses in very large numbers of institutionalized pulmonary patients was below *the average of the general population*.[748] This seems to be due to the sheltered life and the absence of occupational hazards.

Cyanosis is marked in many respiratory diseases. The blue discoloration may be of short duration as for example *in* the whooping cough attack or it may be longer as in diphtheria, some cases of pneumonia, pleuritis, emphysema or large mediastinal tumors.

The frequency of acrocyanosis and erythrocyanosis in a series of about 5000 cases of pulmonary tuberculosis is emphasized by Szanto.[748,3097] Papulonecrotic and indurative tuberculous lesions have been described in connection with acrocyanosis[3098,3099] and livedo racemosa. Women are particularly subject to acrocyanotic conditions which may account for the female dominance in tuberculosis indurativa (erythema induratum).

Telangiectases on the thorax are said to occur in 45 per cent of patients with pulmonary tuberculosis. They are called *Francke's striae*, a misnomer since they are actually telangiectases and not atrophies.[667,748,3100]

These telangiectases are at most 1 cm. long, straight, curved or branched, thin, sharply drawn blood vessels in the skin over the upper dorsal vertebrae and along the costal arch in front of the anterior axillary line. *The latter are* much more common in men (11 per cent), the *former* about equally *frequent* (3 per cent) in both sexes.[748] Francke's striae seem to be independent of the severity of the lung process but more apt to occur in cases of long duration. They are probably due to lung and pleural involvement adjacent to or underlying the respective skin areas. The telangiectases are not characteristic of tuberculosis since they are encountered in normal persons *and also in emphysema*. They are common in elderly men.

Sorgo[3101] found the *skin over parietal pleuritic lesions* thicker and slightly edematous. *It is consistent with this observation that hypodermic injections* of 1 per cent solution *of* congo red into symmetric sites of the thorax showed in 36 out of one hundred patients with pulmonary tuberculosis a larger spot on the diseased side.[31]

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* This chapter includes the ... de madrom s of pulmonary tuberculosis.

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Striae thoracicae in lung disease have been discussed under the heading striae

A rapid course in pulmonary tuberculosis often increases the *succulence* of the skin In chronic cases the skin is more apt to be thin and dry—even diffusely atrophic resembling senile skin Szantó[748] considers these changes as nonspecific and inherent to the severe disease

Fungous diseases are frequent Pityriasis versicolor once considered a characteristic accompaniment of pulmonary tuberculosis has become relatively rare 1 5 per cent [748] This is probably due to better bathing conditions However it is still three times more frequent among the dermatoses of the inmates of lung sanitariums than among the dermatoses of nontuberculous groups The incidence of epidermophytosis is 6 times greater [748] sweating probably being a factor

Many statistics emphasize the high incidence of *acne* among the patients of lung sanitariums The percentages range from 7 per cent [310] over 12 per cent[748] to about 40 per cent [747 3103] However these statistics lack comparable controls in the corresponding age classes of the healthy population Overeating of fats during dietetic treatment may be responsible The more severe acne dorsalis is often found over the site of the greatest pulmonary involvement [747 748] Szantó [48] in his very large series confirms the relatively great frequency severity and incidence in age groups up to 40 and 50 years Exacerbation of acne after artificial pneumothorax has been observed by several authors [747 748] Shoji[3104] found the eyelashes of patients with pulmonary tuberculosis to be longer than those of normal controls Chloasma was found twelve times more frequently than in the general population [748]

Since it had been suspected that pulmonary tuberculosis in *red haired* per sons takes a more rapidly fatal course Bogen[3105] compared a group of red haired persons with the average of 10 000 other patients with pulmonary tuberculosis No significant differences in the fatality rate could be found

The pressure in the *skin capillaries* was found higher in fibrotic pulmonary tuberculosis than in exudative forms [3106] In a series of 241 cases of pulmonary tuberculosis the capillaries of the nailbeds of the fingers on the side of the more active lung lesion were found more dilated than on the other side The side of gross fibrosis and caverns is often marked by deformed capillaries on an anemic background [3107]

Bronchial asthma is sometimes combined with eczema of the flexor surfaces Alternating between eczema and asthma also familial accumulations of both

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conditions is well known The discussion of these relations belongs to the province of allergy

The lunulae of the *fingernails* were found absent from all fingernails five times more frequently in patients with pulmonary tuberculosis than in controls and eleven times more often when the tuberculosis was complicated by silicosis [3108] Heller considers the disappearance of the lunulae an important diagnostic and prognostic sign but it is not rarely seen in healthy person

Clubbing of the fingertips often accompanies chronic pulmonary lesions e g emphysema pulmonary abscess bronchiectasis and carcinoma [558] Clubbing occurs in 17 per cent of cases of chronic pulmonary tuberculosis It seems more



Fig 380 —Clubbed fingers bronchiecta is

common in Negro males than in whites and it indicates a poor prognosis [3109] The terminal phalanges become thicker and the nails larger and curved in both the longitudinal and transverse directions

Pitting of the nails was observed in 100 per cent of a group of patients suffering from active pulmonary tuberculosis as compared with 6 per cent of a group of patients whose disease had been inactive for a relatively short period It was completely absent in patients who were inactive for longer than one year [3110]

Frequent dermadromes of pulmonary tuberculosis are *thickening of the nail plate and longitudinal curving* The latter is known as the *Hippocratic nail* because Hippocrates knew and described the curved nail and its ominous prognostic significance Modern observations [458, 3110] have amply confirmed the high

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incidence (76 per cent[3110]) of Hippocratic curvature in active cases. Szantó[748], however, found only 5.6 per cent among 27,540 patients.

Cyanosis of the distal end of the fingernail bed was noted in 66 per cent of Hahn's group and in 4.2 per cent of Szantó's group of active cases. Differences in the severity of the cases of pulmonary tuberculosis seem to explain the great discrepancy. The cyanosis of the nailbeds is more pronounced in rapidly advancing cases. Ridging, transverse and longitudinal, does not seem to be of prognostic importance.[748]

TABLE II DIFFUSE PIGMENTATIONS

CAUSE	DISTRIBUTION	COLOR	MUCOSAE	ASSOCIATED SYMPTOMS	BLOOD	URINE	PIGMENT	HISTORY COURSE	MISCELLANEOUS
Addison's Disease	Uneven emphasis on normally pigmented areas face neck hands palm nail beds light creases dark	Gray—tan	Slate spots common	Asthenia hypotension dehydration effect of NaCl and cortin thin skin	Hypoglycemia Low NaCl	High NaCl	*Melanin* in basal layer of epidermis also in cutis (melanophores)	Chronic with acute attacks	TB in 90% scars pigmented loss of pubic and axillary hair Depigmentation rare great variability
Exophthalmic Goiter	Addisonian type or chloasma	All degrees	Rare	Vitiligo about 10%					
Malaria	Addisonian type	Gray tan	Rare	Splenomegaly anemia	Plasmodia?				Melanoderma in 15% mostly mild
Tuberculosis	Nipples axillae chloasma Also Addisonian type	Brown	Rare	Cachexia					Rare
Pernicious and other anemias Also Sprue	Addisonian type diffuse in a few per cent	All shades to deep bronzing	Rare	In sprue also patches and small pigm spots besides generalized melanoderma					
Pellagra							Melanin and iron containing pigment	Pigmentation exaggerated by exposure to sun	
Vagabonds Disease	Uneven patchy back belt covered areas more involved than hands or arms	Gray	Occasionally slate spots on buccal mucosa and tongue	Slightly lowered or normal blood pressure Streaky depigmented excoriations Thick skin Pediculosis		Albuminuria common		Vagrancy neglect. Melanoderma heals quickly under hospital care	
	All areas which are able to form increased pigmentation esp face (chloasma) linea alba vulva areola mammae						Melanin		Common Diffuse and severe melanoderma rare

Stilbestrol medication in menarch									
Ovarian Tumors	Similar as in pregnancy								Mild
Ovarian Deficiency	Same				Depression				
Hepatic Cirrhosis	Some tendency in pigment genic areas (nipples etc)								Common
Cushing's syndrom	1 General Addisonian type is inconstant Face 2 Legs frequent hemorrhagic	Dusky copper		Obesity striae diabetes etc			Melanin except for hemosiderin in hemorrhagic lesions		Rare
Vitamin A D ficiency	Diffuse	Dull slate	Conjunctivae esp upper half	Phrynoderma night blindness keratomalacia					Rare
Scurvy (Vit. C)	Diffuse	Generally mild pigmentation					Melanin and hemosiderin	Disappears on treatment with vitamin C	Rare
Hemochromatosis (Bronzed diabetes)	Face genitals, also large covered areas of trunk	Bronze slate often metallic sheen	About 20% have spots Sclerae mostly free	Diabetes mellitus Hepatic cirrhosis. Atrophy of testes Alopecia axillaris and pubica			Melanin and Fe containing pigm.		Rare
Ochronosis	Cartilages of ears nose tendons of musculi recti oculorum show as triangular bluish spots in interpalpebral fissures	Gray slate-black	Very rare	Green to black cerumen		Dark or darkening on air		Prolonged absorption of phenol may cause ochronosis	Rare
Acanthosis Nigricans	Axillary inguinal neck umbilicus, lips vulva	Gray black Rarely non pigmented	Papillary or granulated appearance of oral mucosa	Visceral cancer in older persons frequently internal (endocrine) assoc e g obesity diabetes in juveniles			Engrossed papillae Melanin in basal layer		Rare

TABLE II DIFFUSE PIGMENTATIONS—Continued

CAUSE	DISTRIBUTION	COLOR	MUCOSAE	ASSOCIATED SYMPTOMS	BLOOD	URINE	PIGMENT	HISTORY COURSE	MISCELLANEOUS
Melanoma	Face hands	Bluish black (very rare)							Severe cases extremely rare Slight melanoderma *not rare*
Hodkin s Disease	Addisonian type			Lymphomas			Melanin		In 10% of the cases
Chronic Circulatory Decompensation	Extremities dorsa of hands	Brown		*Cyanosis* symptoms from deficiencies of the cardiac valves and decompensation			Hemosiderin		*Pronounced ca es rare* sl cases common esp in children
Katatonia Schizophrenia and other Psychoses	Addisonian type Sometimes quite dark			Occasional parallelism of pigmentation with course of psychosis					Pronounced cases are rare
Racial	Evenly over body	All shades	Spots diffuse or punctate oral and conjunctival pigmentations common in all races inclined to pigmentation(Mulattoes Mediterraneans Jews Arabs Japanese etc)				Melanin	Ascendency	
Arsenic Arsphenamine	*Diffuse* or in *small spots* mixed with depigmentation raindrops. Trunk pressure points covered parts generally but not always more affected	Gray brown	Usually free	Keratoses polyneuritis etc		As	Melanin not As	Insidious onset May or may not disappear after discontinuation of As	Fowler s solution *Drinking water* Paints Severe melanoderma may follow exfoliative dermatitis from arsphenamine

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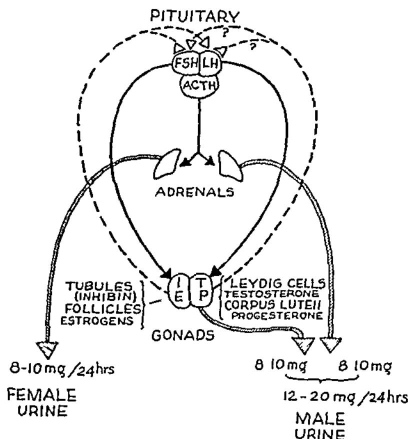


FIG 480 SOURCE OF URINARY 17 KETOSTEROIDS IN MALE AND FEMALE (See also Fig 481) Diagram shows only the immediate factors involved The mechanism of ACTH and production of S' hormones by the adrenal cortices as well as the possible influences of epinephrine and hypothalamus are omitted The 17 ketosteroids in women are frequently higher than illustrated Values of from 15 to 20 mg /24 hrs may be of no clinical significance Note that all 17 ketosteroids are derived from adrenal cortices while about 50% in males come from the testes

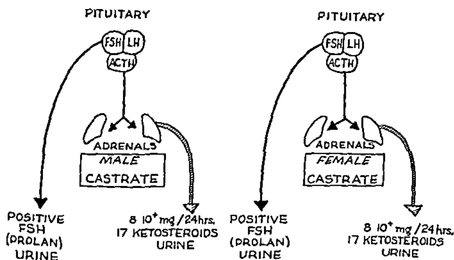


FIG 481 17 KETOSTEROIDS IN CASTRATES 17 ketosteroids in castrated or menopausal women are not significantly changed but are approximately decreased by half in males at least temporarily Urinary FSH is increased



Fig 482 Effect of Testosterone on Discoid Lupus Erythematosus *(Left)* Age 36 Male Biopsy findings were consistent with discoid lupus Testosterone propionate 100 mg daily for 23 days then free testosterone suspension 25 mg intramuscularly daily for 48 days *(Right)* All lesions cleared and improvement has been maintained on 12 mg of testosterone locally for 2 months (Fromer L C The use of testosterone in chronic lupus erythematosus preliminary report Lahey Clin Bull 7 13 1/)

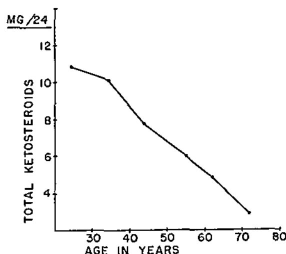


Chart 143 Total 17 ketosteroids Progressive decrease in the excretion of urinary 17 ketosteroids with aging (Hamilton H B and Hamilton J B Aging in apparently normal men I Urinary titers of ketosteroids and of alpha hydroxy and beta hydroxy ketosteroids J Clin Endocrinol 8 433-452)

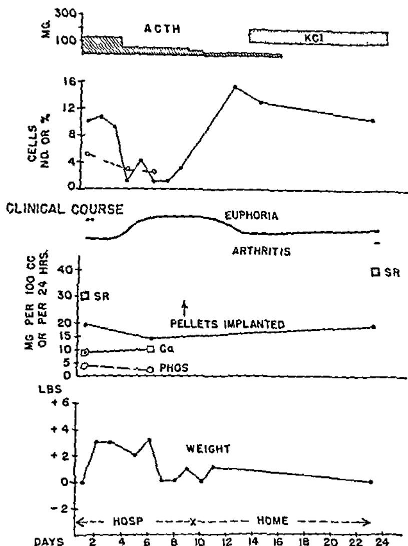


CHART 144 EFFECT OF ACTH IN A PATIENT WITH HYPOPITUITARISM MILD DIABETES INSIPIDUS AND RHEUMATOID ARTHRITIS Age 63 female patient who had an operation for the removal of a cranio-pharyngioma about a year before Eosinophils (solid line with block dots) did not fall until fourth day Per cent of lymphocytes (broken line open circles) was also decreased Recurrence of joint ymptoms developed slowly after omitting ACTH for several weeks Pellets of te tosterone (300 mg) and desoxycorticosterone acetate (150 mg) had previously benefited patient without improving her arthritis All joint symptoms disappeared on read ministration of ACTH and patient had been maintained in excellent health on 20 mg ACTH every other day for 6 months when it was discontinued No return of arthritis after 2 years Polydipsia and polyuria (7 to 8 liters daily) were only mildly ameliorated on larger doses of ACTH but on maintenance doses the same amount of pitressin was required to control these symptoms

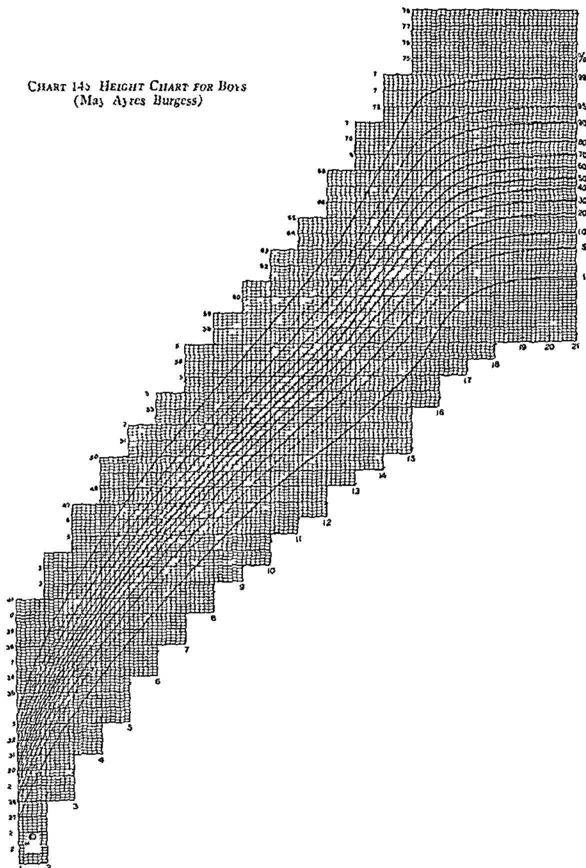
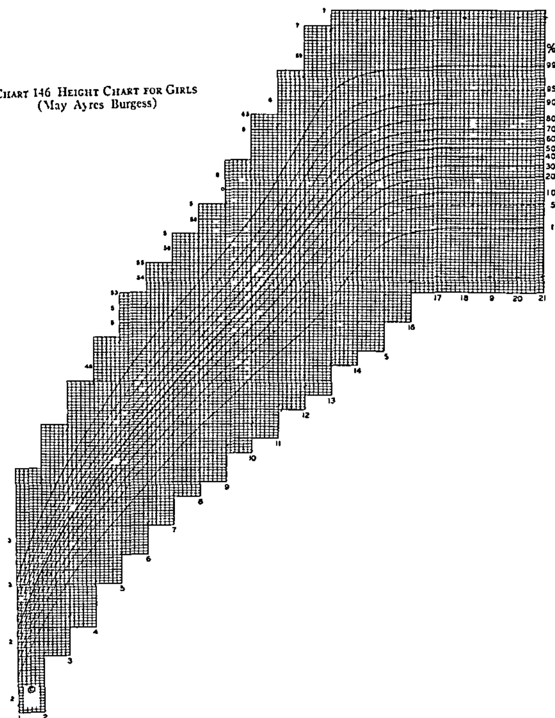


CHART 145 HEIGHT CHART FOR BOYS
(May Ayres Burgess)

Chart 146 Height Chart for Girls
(May Ayres Burgess)



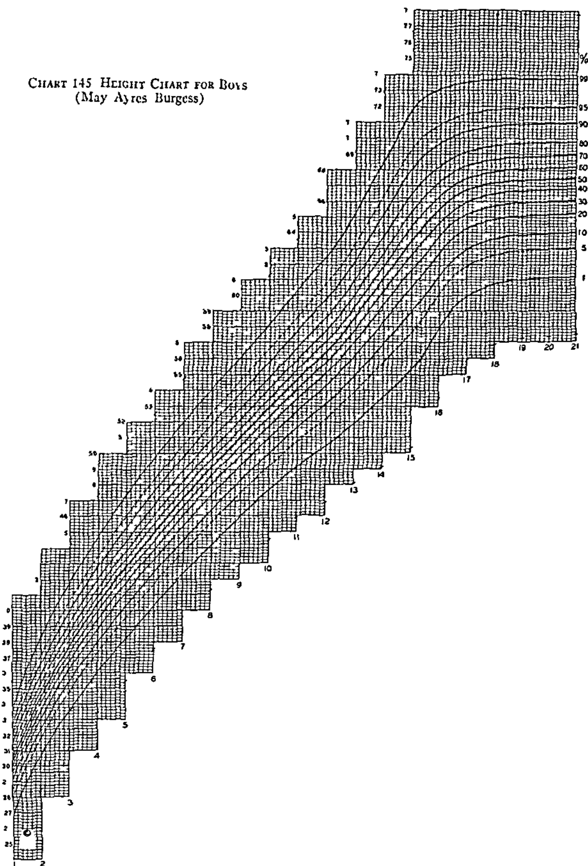


CHART 145 HEIGHT CHART FOR BOYS
(May Ayres Burgess)

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